ClinicalEvidence

Acne vulgaris

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ABSTRACT

INTRODUCTION: Acne vulgaris affects over 80% of teenagers, and persists beyond the age of 25 years in 3% of men and 12% of women. Typical lesions of acne include comedones, inflammatory papules, and pustules. Nodules and cysts occur in more severe acne and can cause scarring and psychological distress. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical question: What are the effects of topical and oral treatments in people with acne vulgaris? We searched: Medline, Embase, The Cochrane Library, and other important databases up to February 2010 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 69 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: topical treatments (adapalene, azelaic acid, benzoyl peroxide, clindamycin, erythromycin [alone or plus zinc]; isotretinoin, tetracycline, tretinoin); and oral treatments (doxycycline, isotretinoin, lymecycline, minocycline, oxytetracycline, tetracycline).

QUESTIONS

INTERVENTIONS

Key points

- Acne vulgaris affects over 80% of teenagers, and persists beyond the age of 25 years in 3% of men and 12% of women.

  Typical lesions of acne include comedones, inflammatory papules, and pustules. Nodules and cysts occur in more severe acne, and can cause scarring and psychological distress.

- Topical benzoyl peroxide should be considered as first-line treatment in mild acne.

  Topical benzoyl peroxide and topical azelaic acid reduce inflammatory and non-inflammatory lesions compared with placebo, but can cause itching, burning, stinging, and redness of the skin.

- Topical antibiotics such as clindamycin and erythromycin (alone or with zinc) reduce inflammatory lesions compared with placebo, but have not been shown to reduce non-inflammatory lesions. Tetracycline may reduce overall acne severity.

  Antimicrobial resistance can develop with use of topical or oral antibiotics, and their efficacy may decrease over time.

  Tetracyclines may cause skin discoloration, and should be avoided in pregnant or breastfeeding women.

Topical preparations of tretinoin, adapalene, and isotretinoin may reduce inflammatory and non-inflammatory lesions, but can also cause redness, burning, dryness, and soreness of the skin.

- Oral antibiotics (doxycycline, erythromycin, lymecycline, minocycline, oxytetracycline, and tetracycline) are considered useful for people with more severe acne, although we don't know for sure whether they are effective.

  Oral antibiotics can cause adverse effects such as contraceptive failure.

  Minocycline has been associated with an increased risk of systemic lupus erythematosus and liver disorders.

  Oral isotretinoin has been associated with skin problems, change in liver function, teratogenesis, and psychiatric disorders.

DEFINITION

Acne vulgaris is a common inflammatory pilosebaceous disease characterised by comedones; papules; pustules; inflamed nodules; superficial pus-filled cysts; and (in extreme cases) canalising and deep, inflamed, sometimes purulent sacs. [1] Lesions are most common on the face, but the neck, chest, upper back, and shoulders may also be affected. Acne can cause scarring and considerable psychological distress. [2] It is classified as mild, moderate, or severe. [1] **Mild acne** is defined as non-inflammatory lesions (comedones), a few inflammatory (papulopustular) lesions, or both. **Moderate acne** is defined as more inflammatory lesions, occasional nodules, or both, and mild scarring. **Severe acne** is defined as widespread inflammatory lesions, nodules, or both, and scarring, moderate acne that has not settled with 6 months of treatment, or acne of any "severity" with serious psychological upset. This review does not cover acne rosacea, acne secondary to industrial occupations, and treatment of acne in people under 13 years of age.

INCIDENCE/ PREVALENCE

Acne is the most common skin disease of adolescence, affecting over 80% of teenagers (aged 13–18 years) at some point. [3] Estimates of prevalence vary depending on study populations and the method of assessment used. Prevalence of acne in a community sample of 14- to 16-year-olds in the UK has been recorded as 50%. [4] In a sample of adolescents from schools in New Zealand, acne was present in 91% of males and 79% of females, and in a similar population in Portugal the prevalence was 82%. [5] [6] It has been estimated that up to 30% of teenagers have acne of sufficient severity to require medical treatment. [7] Acne was the presenting complaint in 3.1% of people aged 13 to 25 years attending primary care in a UK population. [8] Overall incidence is similar in both men and women, and peaks at 17 years of age. [7] The number of adults with acne, including people over 25 years, is increasing; the reasons for this increase are uncertain. [9]

AETIOLOGY/ RISK FACTORS

The exact cause of acne is unknown. Four factors contribute to the development of acne: increased sebum secretion rate, abnormal follicular differentiation causing obstruction of the pilosebaceous duct, bacteriology of the pilosebaceous duct, and inflammation. [10] The anaerobic bacterium *Propionibacterium acnes* plays an important role in the pathogenesis of acne. Androgen secretion is the major trigger for adolescent acne. [11]

PROGNOSIS

In 3% of men (95% CI 1.2% to 4.8%) and 12% of women (95% CI 9% to 15%), facial acne persists after the age of 25 years, [12] and in a few people (1% of men and 5% of women) acne persists into their 40s. [9]

AIMS OF INTERVENTION

To reduce the number of non-inflammatory and inflammatory lesions and scarring, with minimal adverse effects of treatment.

OUTCOMES

Acne severity: as measured by number of non-inflammatory lesions (comedones), number of inflammatory lesions (papules, pustules, and nodules), severity scores and scales; **patient perception of improvement**; **psychological distress**; **quality of life**; and **adverse effects** of treatment. Commonly used severity scores and scales include: Leeds Acne Grading Technique, which involves counting and categorising lesions into inflammatory and non-inflammatory; [13] Cook's acne grading scale method, which uses photographs to document severity of acne and grades severity from 0 (least severe) to 8 (most severe); [14] and the Pillsbury Scale, which classifies acne from 1 (mildest) to 4 (severe). [15]

METHODS

Clinical Evidence search and appraisal February 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to February 2010, Embase 1980 to February 2010, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and

RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. The review by Lehmann et al [16] included both randomised and non-randomised controlled trials, and did not state in all cases whether trials were randomised. We have focused on reporting results for RCTs only and, where necessary, have analysed original papers to ascertain whether trials were randomised. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA), which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 69). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of topical treatments in people with acne vulgaris?

OPTION BENZOYL PEROXIDE (TOPICAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Topical benzoyl peroxide should be considered as first-line treatment in mild acne.
- Topical benzoyl peroxide and topical azelaic acid reduce inflammatory and non-inflammatory lesions compared with placebo, but can cause itching, burning, stinging, and redness of the skin.

Benefits and harms

Topical benzoyl peroxide versus placebo:

We found two systematic reviews comparing topical benzoyl peroxide acid versus placebo (vehicle). [16] [17] The first review (search date 1999, 5 RCTs) did not perform a meta-analysis owing to heterogeneity among the trials in methods of outcome assessment. [16] The second review (search date 2004), [17] which had more stringent inclusion criteria than the earlier review, included one RCT, [18] which was also identified by the earlier review.

Acne severity

Topical benzoyl peroxide compared with placebo Topical benzoyl peroxide may be more effective at reducing the total lesion count or the number of inflammatory and non-inflammatory lesions at 4 to 12 weeks in people with moderate acne (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Total lesion count/severity					
[19] RCT **4-armed trial**	196 people with moderate acne In review [16] The remaining arms evaluated benzoyl peroxide plus chlorhydroxyquinolone and benzoyl peroxide plus chlorhydroxyquinolone plus hydrocortisone	**Percentage reduction in total lesion count , 4 weeks** 37% with benzoyl peroxide 5.5% 4 times daily 6% with vehicle	P = 0.001 for benzoyl peroxide *v* vehicle	○○○	Benzoyl peroxide

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] RCT **3-armed trial**	150 people with mild to moderate acne In review [16] The remaining arm evaluated gluconolactone 14%	**Reduction in total lesion count from baseline , 12 weeks** with benzoyl peroxide 5% with vehicle Benzoyl peroxide significantly reduced total lesion count from baseline (P <0.01)	No direct comparison between benzoyl peroxide and vehicle		
[20] RCT **3-armed trial**	77 people with mild to moderate acne In review [16] The remaining arm evaluated isotretinoin	**Leeds severity score (where 0 = no acne and 10 = severest acne) , 12 weeks** 0 with benzoyl peroxide 5% 1 with vehicle	P <0.05 for benzoyl peroxide *v* vehicle	○○○	Benzoyl peroxide
[21] RCT	59 people with mild to moderate acne In review [16]	**Proportion of people with "good" (51–75% reduction) or "excellent" (76–100% reduction) response , 12 weeks** 19/26 (73%) with benzoyl peroxide 20% 10/25 (40%) with vehicle	P <0.05	○○○	Benzoyl peroxide
Non-inflammatory lesions					
[18] RCT **4-armed trial**	393 people with moderate acne In review [16] [17] The remaining arms evaluated clindamycin and benzoyl peroxide plus clindamycin	**Percentage change in non-inflammatory lesions , 11 weeks** –30% with benzoyl peroxide 5% +11% with vehicle	P <0.005 for benzoyl peroxide *v* vehicle	○○○	Benzoyl peroxide
[22] RCT **3-armed trial**	150 people with mild to moderate acne In review [16] The remaining arm evaluated gluconolactone 14%	**Reduction in non-inflammatory lesions from baseline , 12 weeks** with benzoyl peroxide 5% with vehicle Benzoyl peroxide significantly reduced the number of non-inflammatory lesions from baseline (P <0.05)	No direct comparison between benzoyl peroxide and vehicle		
[20] RCT **3-armed trial**	77 people with mild to moderate acne In review [16] The remaining arm evaluated isotretinoin	**Mean percentage change in number of non-inflammatory lesions** –52% with benzoyl peroxide 5% +6% with vehicle	P = 0.01 for benzoyl peroxide *v* vehicle	○○○	Benzoyl peroxide
Inflammatory lesions					
[18] RCT **4-armed trial**	393 people with moderate acne In review [16] [17] The remaining arms evaluated clindamycin and benzoyl peroxide plus clindamycin	**Percentage reduction in inflammatory lesions , 11 weeks** 39% with benzoyl peroxide 5% 5% with vehicle	P <0.002 for benzoyl peroxide *v* vehicle	○○○	Benzoyl peroxide

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[22] RCT **3-armed trial**	150 people with mild to moderate acne In review [16] The remaining arm evaluated gluconolactone 14%	**Reduction in inflammatory lesions from baseline , 12 weeks** with benzoyl peroxide 5% with vehicle Benzoyl peroxide significantly reduced the number of inflammatory lesions from baseline (P <0.02)	No direct comparison between benzoyl peroxide and vehicle		
[20] RCT **3-armed trial**	77 people with mild to moderate acne In review [16] The remaining arm evaluated isotretinoin	**Mean percentage change in number of inflammatory lesions** –52% with benzoyl peroxide 5% +9% with vehicle	P = 0.01 for benzoyl peroxide *v* vehicle	○○○	Benzoyl peroxide

Patient perception of improvement

No data from the following reference on this outcome. [19] [18] [22] [20] [21]

Psychological distress

No data from the following reference on this outcome. [19] [18] [22] [20] [21]

Quality of life

No data from the following reference on this outcome. [19] [18] [22] [20] [21]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Skin irritation					
[19] RCT **4-armed trial**	196 people with moderate acne In review [16] The remaining arms evaluated benzoyl peroxide plus chlorhydroxyquinolone and benzoyl peroxide plus chlorhydroxyquinolone plus hydrocortisone	**Adverse effects , 4 weeks** with benzoyl peroxide 5.5% 4 times daily with vehicle RCT suggested that peeling and erythema were "negligible" in all groups, but gave no quantitative information about adverse effects			
[18] RCT **4-armed trial**	393 people with moderate acne In review [16] [17] The remaining arms evaluated	**Peeling , 11 weeks** 21% with benzoyl peroxide 5% 15% with vehicle	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	clindamycin and benzoyl peroxide plus clindamycin				
[22] RCT **3-armed trial**	150 people with mild to moderate acne In review [16] The remaining arm evaluated gluconolactone 14%	**Adverse effects , 12 weeks** 22/75 (29%) with benzoyl peroxide 5% 5/75 (7%) with vehicle Adverse effects included dryness, scaling, burning, tingling, and redness	P = 0.05	○○○	Vehicle
[20] RCT **3-armed trial**	77 people with mild to moderate In review [16] The remaining arm evaluated isotretinoin	**Adverse effects , 12 weeks** with benzoyl peroxide 5% with vehicle Benzoyl peroxide was associated with erythema, dryness, soreness, and burning; one person taking benzoyl peroxide withdrew because of adverse effects			
[21] RCT	59 people with mild to moderate acne In review [16]	**Redness and peeling , 12 weeks** 21/29 (72%) with benzoyl peroxide 20% 17/30 (57%) with vehicle	Significance not assessed		

Further information on studies

Comment: **Clinical guide:**
Benzoyl peroxide is indicated as an effective first-line treatment for mild acne. It has antimicrobial and anticomedonal properties, in addition to an anti-inflammatory effect. It is recommended to start with a lower strength and increase gradually. Reducing frequency of application or temporarily discontinuing treatment helps with irritation.

OPTION CLINDAMYCIN (TOPICAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Topical antibiotics such as clindamycin reduce inflammatory lesions compared with placebo, but have not been shown to reduce non-inflammatory lesions.
- Antimicrobial resistance can develop with use of topical or oral antibiotics, and their efficacy may decrease over time.

Benefits and harms

Topical clindamycin versus placebo:

We found two systematic reviews. [16] [17] The first review (search date 1999, 7 RCTs, [18] [23] [24] [25] [26] [27] [28] 1502 people with mild to severe acne) compared topical clindamycin 1% (phosphate or hydrochloride) 1 to 4 times daily versus placebo or vehicle for 8 to 12 weeks. [16] The review did not perform a meta-analysis owing to heterogeneity among the trials in comparisons and outcomes assessed. The second systematic review (search date 2004), which had more stringent inclusion criteria, identified two RCTs, [18] [27] both of which were identified by the earlier review.

Acne severity

Topical clindamycin compared with placebo/vehicle Topical clindamycin may be more effective at reducing the number of inflammatory lesions at 8 to 12 weeks in people with mild to severe acne, but we don't know whether it is more effective at reducing total lesion count or non-inflammatory lesions (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Total lesion count					
[28] RCT	46 people with moderate to severe acne In review [16] [17]	**Mean lesion count , 12 weeks** 0.2 with clindamycin phosphate 1% twice daily 0.6 with placebo	P = 0.34	⟷	Not significant
Non-inflammatory lesions					
[18] RCT **4-armed trial** Pooled data from one single-centre and one multicentre trial	393 people with moderate acne In review [16] [17] The remaining arms evaluated benzoyl peroxide 5% and benzoyl peroxide plus clindamycin	**Mean percentage change in non-inflammatory lesions from baseline , 11 weeks** –9% with clindamycin 1% 4 times daily +11% with vehicle 4 times daily	P = 0.04 for clindamycin *v* vehicle	○○○	Clindamycin
[25] RCT	40 people with mild to moderate acne In review [16]	**Percentage reduction in open comedones , 12 weeks** 38% with clindamycin phosphate 1% twice daily 32% with placebo Only 76% of people completed the trial, but intention-to-treat analysis was performed	Reported as not significant P value not reported	⟷	Not significant
[28] RCT	46 people with moderate to severe acne In review [16] [17]	**Mean number of open comedones per person , 12 weeks** 3.3 with clindamycin phosphate 1% twice daily 5.2 with placebo	P = 0.49	⟷	Not significant
[28] RCT	46 people with moderate to severe acne In review [16] [17]	**Mean number of closed comedones per person , 12 weeks** 3.4 with clindamycin phosphate 1% twice daily 5.1 with placebo	P = 0.47	⟷	Not significant
Inflammatory lesions					
[18] RCT **4-armed trial** Pooled data from one single-centre and one multicentre trial	393 people with moderate acne In review [16] [17] The remaining arms evaluated benzoyl peroxide 5% and benzoyl peroxide plus clindamycin	**Mean percentage reduction in inflammatory lesions from baseline , 11 weeks** 35% with clindamycin 1% 4 times daily 5% with vehicle 4 times daily	P <0.001 for clindamycin *v* vehicle	○○○	Clindamycin
[23] RCT **3-armed trial**	108 people with mild to moderate acne In review [16]	**Mean reduction in inflammatory lesion count (change from baseline) , 8 weeks** From 8.52 to 2.38 with clindamycin	No direct comparison of topical clindamycin *v* placebo RCT designed to compare topical clindamycin *v* oral tetracycline		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm evaluated oral tetracycline 500 mg twice daily	From 7.10 to 6.24 with placebo 87 people in this analysis (completer analysis); intention-to-treat analysis not performed P = 0.0001 for reduction in lesion count from baseline with clindamycin Reduction in lesion count from baseline with placebo reported as not significant (P value not reported)			
[25] RCT	40 people with mild to moderate acne In review [16]	**Percentage reduction in papules , 12 weeks** 22% with clindamycin phosphate 1% twice daily 19% with placebo Only 76% of people completed the trial, but intention-to-treat analysis was performed	Reported as not significant P value not reported	⟷	Not significant
[25] RCT	40 people with mild to moderate acne In review [16]	**Percentage reduction in pustules , 12 weeks** 12% with clindamycin phosphate 1% twice daily 22% with placebo Only 76% of people completed the trial, but intention-to-treat analysis was performed	Reported as not significant P value not reported	⟷	Not significant
[26] RCT **3-armed trial**	367 people with moderate to severe acne In review [16] The remaining arm evaluated oral tetracycline	**Mean number of papules per person , 8 weeks** 8.3 with clindamycin 11.7 with placebo Completer analysis of 305/367 (83%) people who completed the trial	P <0.05 for clindamycin *v* placebo	○○○	Clindamycin
[26] RCT **3-armed trial**	367 people with moderate to severe acne In review [16] The remaining arm evaluated oral tetracycline	**Mean number of pustules per person , 8 weeks** 1.1 with clindamycin 2.7 with placebo Completer analysis of 305/367 (83%) people who completed the trial	P <0.05 for clindamycin *v* placebo	○○○	Clindamycin
[27] RCT **3-armed trial**	413 people with moderate acne In review [16] [17] The third arm evaluated clindamycin hydrochloride 1% twice daily	**Percentage reduction in papules , 8 weeks** 56% with clindamycin phosphate 1% twice daily 42% with vehicle Analysis of 358/413 (87%) people who completed the trial	P = 0.05 or less for clindamycin phosphate *v* vehicle	○○○	Clindamycin
[27] RCT **3-armed trial**	413 people with moderate acne In review [16] [17] The third arm evaluated clindamycin phosphate 1% twice daily	**Percentage reduction in papules , 8 weeks** 64% with clindamycin hydrochloride 1% twice daily 42% with vehicle Analysis of 358/413 (87%) people who completed the trial	P = 0.05 or less for clindamycin hydrochloride *v* vehicle	○○○	Clindamycin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[27] RCT **3-armed trial**	413 people with moderate acne In review [16] [17] The third arm evaluated clindamycin hydrochloride 1% twice daily	**Percentage reduction in pustules , 8 weeks** 72% with clindamycin phosphate 1% twice daily 43% with vehicle Analysis of 358/413 (87%) people who completed the trial	P = 0.05 or less for clindamycin phosphate *v* vehicle	○○○	Clindamycin
[27] RCT **3-armed trial**	413 people with moderate acne In review [16] [17] The third arm evaluated clindamycin phosphate 1% twice daily	**Percentage reduction in pustules , 8 weeks** 62% with clindamycin hydrochloride 1% twice daily 43% with vehicle Analysis of 358/413 (87%) people who completed the trial	Significance not assessed		
[28] RCT	46 people with moderate to severe acne In review [16] [17]	**Mean number of pustules per person , 12 weeks** 1.5 with clindamycin phosphate 1% twice daily 3.1 with placebo	P = 0.02	○○○	Clindamycin
[28] RCT	46 people with moderate to severe acne In review [16] [17]	**Mean number of papules per person , 12 weeks** 6.8 with clindamycin phosphate 1% twice daily 10.6 with placebo	P = 0.16	⟷	Not significant

Patient perception of improvement

Topical clindamycin compared with placebo/vehicle Topical clindamycin may be more effective at increasing the proportion of people with mild to severe acne who rate their acne as markedly improved or improved (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient perception of improvement					
[23] RCT **3-armed trial**	108 people with mild to moderate acne In review [16] The remaining arm evaluated oral tetracycline 500 mg twice daily	**Proportion of people whose acne had "markedly improved" or "improved" from baseline , 8 weeks** 72% with clindamycin 3% with placebo 87 people in this completer analysis; intention-to-treat analysis not performed	No direct comparison of topical clindamycin *v* placebo RCT designed to compare topical clindamycin *v* oral clindamycin		
[26] RCT **3-armed trial**	367 people with moderate to severe acne In review [16] The remaining arm evaluated oral tetracycline	**Proportion of people who thought their acne was "markedly improved" or "improved" , 8 weeks** 88% with clindamycin 57% with placebo Completer analysis of 305/367 (83%) people who completed the trial	P <0.05 for clindamycin *v* placebo	○○○	Clindamycin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[27] RCT **3-armed trial**	413 people with moderate acne, 8 weeks In review [16] [17] The third arm evaluated clindamycin hydrochloride 1% twice daily	**Proportion of people who rated acne "markedly improved" or "improved" compared with vehicle , 8 weeks** 77% with clindamycin phosphate 1% twice daily 56% with vehicle Analysis of 358/413 (87%) people who completed the trial	Difference for clindamycin phosphate versus placebo reported as significant P value not reported	○○○	Clindamycin
[27] RCT **3-armed trial**	413 people with moderate acne, 8 weeks In review [16] [17] The third arm evaluated clindamycin phosphate 1% twice daily	**Proportion of people who rated acne "markedly improved" or "improved" compared with vehicle , 8 weeks** 77% with clindamycin hydrochloride 1% twice daily 56% with vehicle Analysis of 358/413 (87%) people who completed the trial	Difference for clindamycin hydrochloride versus placebo reported as significant P value not reported	○○○	Clindamycin

No data from the following reference on this outcome. [18] [25] [28]

Psychological distress

No data from the following reference on this outcome. [18] [23] [25] [26] [27] [28]

Quality of life

No data from the following reference on this outcome. [18] [23] [25] [26] [27] [28]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[18] RCT **4-armed trial** Pooled data from one single-centre and one multicentre trial	393 people with moderate acne In review [16] [17] The remaining arms evaluated benzoyl peroxide 5% and benzoyl peroxide plus clindamycin	**Adverse effects (erythema, dryness, peeling, burning, or pruritus) , 11 weeks** with clindamycin 1% 4 times daily with vehicle 4 times daily	Reported as not significant P value not reported	⟷	Not significant
[23] RCT **3-armed trial**	108 people with mild to moderate acne	**Adverse effects , 8 weeks** with clindamycin with placebo			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [16] The remaining arm evaluated oral tetracycline 500 mg twice daily	One person using clindamycin, and one using placebo had diarrhoea 87 people in this completer analysis Intention-to-treat analysis not performed			
[26] RCT **3-armed trial**	367 people with moderate to severe acne In review [16] The remaining arm evaluated oral tetracycline	**Adverse effects , 8 weeks** with clindamycin with placebo 9 people taking clindamycin and 6 people taking placebo had diarrhoea Completer analysis of 305/367 (83%) people who completed the trial			
[27] RCT **3-armed trial**	413 people with moderate acne In review [16] [17]	**Adverse effects , 8 weeks** with clindamycin phosphate 1% twice daily with clindamycin hydrochloride 1% twice daily with vehicle 12 people taking clindamycin and 2 people taking placebo had diarrhoea Completer analysis in 358/413 (87%) people who completed the trial			
[28] RCT	46 people with moderate to severe acne In review [16] [17]	**Adverse effects , 12 weeks** with clindamycin phosphate 1% twice daily with placebo 3 people taking clindamycin and 5 taking placebo had diarrhoea. One person taking clindamycin had burning and one had eczema			

No data from the following reference on this outcome. [25]

Further information on studies

Comment: The review [16] identified one open-label RCT, which did not meet *Clinical Evidence* inclusion criteria (135 people with moderate acne), [24] which found that clindamycin significantly reduced papules and pustules at 12 weeks compared with placebo. It found that clindamycin was associated with burning.

Studies of development of bacterial resistance to antibiotics suggest that topical application of antibiotics in acne may result in antibiotic resistance to *Propionibacterium acnes*. [7] [29] One systematic review (search date 2003) analysed the efficacy of topical antibiotics in clinical trials (randomised and non-randomised) conducted between 1966 and 2003 using linear regression. [30] It found no significant change in the efficacy of 12 weeks' treatment with topical clindamycin 1.0% to 1.2% for

inflammatory or non-inflammatory lesion count over this period (inflammatory lesions: 8 studies, change in efficacy [regression coefficient]: +0.2%/year, P = 0.7; non-inflammatory lesions: 7 studies, change in efficacy: –0.3%/year, P = 0.7). [30]

Clinical guide:
Topical antibiotics or topical retinoids are indicated as treatments for mild acne that does not respond to benzoyl peroxide. Within the antibiotic class, there is more evidence of benefit with topical clindamycin or erythromycin than with erythromycin plus zinc or tetracycline. A conjoint analysis study of patient preference for different topical antibiotic characteristics found that acne patients preferred a gel formulation that could be applied with the fingers once daily and stored at room temperature for up to 18 months. [31]

OPTION ERYTHROMYCIN (TOPICAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Topical antibiotics, such as erythromycin, reduce inflammatory lesions compared with placebo, but have not been shown to reduce non-inflammatory lesions.
- Antimicrobial resistance can develop with use of topical or oral antibiotics, and their efficacy may decrease over time.

Benefits and harms

Topical erythromycin versus placebo:

We found two systematic reviews. [16] [17] The first review (search date 1999, 8 RCTs, [32] [33] [34] [35] [36] [37] [38] [39] 347 people with mild to moderate acne, 555 people with moderate to severe acne) compared topical erythromycin 1% to 2% versus vehicle for 4 to 12 weeks. [16] The review did not perform a meta-analysis owing to heterogeneity among the trials in outcomes assessed. The second systematic review (search date 2004), [17] which had more stringent inclusion criteria, included 3 RCTs, all of which were identified by the earlier review. [33] [35] [36]

Acne severity

Topical erythromycin compared with placebo Topical erythromycin may be more effective at reducing inflammatory lesions at 8 to 12 weeks in people with mild to severe acne (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall severity					
[32] RCT **4-armed trial**	160 people with mild to moderate acne In review [16] The remaining arms evaluated isotretinoin 0.05% alone and isotretinoin plus erythromycin	**Mean percentage change in total lesion count from baseline , 12 weeks** –25% (95% CI –39.04% to –11.44%) with erythromycin 2% –11% (95% CI –24.29% to +2.65%) with placebo	No direct comparison between erythromycin alone and placebo		
[33] RCT	225 people with mild to moderate acne In review [16] [17]	**Reduction in Cook's severity score , 12 weeks** –40 with erythromycin 2% twice daily –22 with vehicle	Reported as not significant P value not reported	⟷	Not significant
[35] RCT	175 people with moderate to severe acne unresponsive to oral tetracycline, topical benzoyl peroxide, or topical tretinoin In review [16] [17]	**Proportion of people rated by physician as having "excellent" or "good" response , 12 weeks** 62% with erythromycin 2% 27% with vehicle Physician rating scale included "excellent", "good", "partially improved", "not improved", and "worse". Unclear how ratings were measured	P <0.001	○○○	Erythromycin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Completer analysis in 156 people; no intention-to-treat analysis. People excluded from analysis for poor compliance and failure to complete treatment			
[36] RCT	253 people with moderate to severe acne In review [16] [17]	**Total lesion count , 12 weeks** with erythromycin 1.5% twice daily with vehicle Absolute results reported graphically	P = 0.01	○○○	Erythromycin
[37] RCT	26 people with moderate to severe acne In review [16]	**Proportion of people rated by physician as having "excellent" or "good" response , 12 weeks** 92% with erythromycin 1.5% twice daily 20% with vehicle	P = 0.005	○○○	Erythromycin
Non-inflammatory lesions					
[32] RCT **4-armed trial**	160 people with mild to moderate acne In review [16] The remaining arms evaluated isotretinoin 0.05% alone and isotretinoin plus erythromycin	**Mean percentage change in non-inflammatory lesions from baseline , 12 weeks** –17% (95% CI –38.07% to +4.63%) with erythromycin 2% –7% (95% CI –28.31% to +14.16%) with placebo	No direct comparison between erythromycin alone and placebo		
[37] RCT	26 people with moderate to severe acne In review [16]	**Comedones , 12 weeks** with erythromycin with vehicle Absolute results not reported The RCT reported that erythromycin had less effect on comedones No further data were reported			
[34] RCT	187 people with mild to moderate acne In review [16]	**Mean reduction in open comedones per person , 8 weeks** –7.5 with erythromycin 2% twice daily –4.6 with vehicle	P <0.01	○○○	Erythromycin
[34] RCT	187 people with mild to moderate acne In review [16]	**Mean reduction in closed comedones per person , 8 weeks** –1.7 with erythromycin 2% twice daily –2.3 with vehicle	Reported as not significant P value not reported	⟷	Not significant
[36] RCT	253 people with moderate to severe acne In review [16] [17]	**Open or closed comedones , 12 weeks** with erythromycin 1.5% twice daily with vehicle Absolute results reported graphically	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Inflammatory lesions					
[32] RCT **4-armed trial**	160 people with mild to moderate acne In review [16] The remaining arms evaluated isotretinoin 0.05% alone and isotretinoin plus erythromycin	**Mean percentage change in inflammatory lesions from baseline , 12 weeks** –28% (95% CI –41.29% to –14.14%) with erythromycin 2% –10% (95% CI –24.51% to +5.36%) with placebo	No direct comparison between erythromycin alone and placebo		
[33] RCT	225 people with mild to moderate acne In review [16] [17]	**Percentage reduction in inflammatory lesions , 12 weeks** 46% with erythromycin 2% twice daily 19% with vehicle	P = 0.01	○○○	Erythromycin
[34] RCT	187 people with mild to moderate acne In review [16]	**Mean reduction in papules per person , 8 weeks** –6.2 with erythromycin 2% twice daily –4.3 with vehicle	P <0.01	○○○	Erythromycin
[34] RCT	187 people with mild to moderate acne In review [16]	**Mean reduction in pustules per person , 8 weeks** –1.7 with erythromycin 2% twice daily –1.2 with vehicle	Reported as not significant P value not reported	⟷	Not significant
[35] RCT	175 people with moderate to severe acne unresponsive to oral tetracycline, topical benzoyl peroxide, or topical tretinoin In review [16] [17]	**Total inflammatory lesion count , 12 weeks** 856 with erythromycin 2% 1338 with vehicle Completer analysis of 156 people; no intention-to-treat analysis. People excluded from analysis for poor compliance and failure to complete treatment	P <0.01	○○○	Erythromycin
[36] RCT	253 people with moderate to severe acne In review [16] [17]	**Papules and pustules , 12 weeks** with erythromycin 1.5% twice daily with vehicle Absolute results reported graphically	P <0.025	○○○	Erythromycin
[37] RCT	26 people with moderate to severe acne In review [16]	**Proportion of people who had more than 50% reduction in papules , 12 weeks** 11/12 (92%) with erythromycin 4/10 (40%) with vehicle	P = 0.01	○○○	Erythromycin
[27] RCT Split-face study	28 people with moderate to severe acne In review [16]	**Reduction in inflammatory lesions , 4 to 8 weeks** with erythromycin 1% twice daily with vehicle In 21 people, erythromycin was more effective than vehicle in reducing inflammatory lesions at 8 weeks, in 4 people vehicle was	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		more effective, and in 3 there was no difference			
[39] RCT Split-face study	73 people with moderate to severe acne In review [16]	**Proportion of people who had more than 50% reduction in inflammatory lesions , 12 weeks** 30% with erythromycin 2% twice daily 20% with vehicle	Reported as not significant P value not reported	⟷	Not significant

Patient perception of improvement

Topical erythromycin compared with placebo We don't know whether topical erythromycin is more effective at increasing the proportion of people with mild to moderate acne who perceive their acne as improved at 12 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient perception of improvement					
[32] RCT **4-armed trial**	160 people with mild to moderate acne In review [16] The remaining arms evaluated isotretinoin 0.05% alone and isotretinoin plus erythromycin	**Proportion of people who perceived that their acne had improved from baseline , 12 weeks** 58% with erythromycin 2% 53% with placebo	Significance not assessed		

Psychological distress

No data from the following reference on this outcome. [32] [33] [34] [35] [36] [37] [38] [39]

Quality of life

No data from the following reference on this outcome. [32] [33] [34] [35] [36] [37] [38] [39]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[35] RCT	175 people with moderate to severe acne unresponsive to oral tetracycline, topical benzoyl peroxide, or topical tretinoin In review [16] [17]	**Proportion of people with one or more adverse effects, including redness, scaling, dryness, and pruritus , 12 weeks** 17/90 (19%) with erythromycin 2% twice daily 21/85 (25%) with vehicle 2 people taking erythromycin withdrew because of adverse ef-	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		fects compared with 4 taking vehicle			
[33] RCT	225 people with mild to moderate acne In review [16] [17]	**Erythema , 12 weeks** with erythromycin 2% twice daily with vehicle Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[33] RCT	225 people with mild to moderate acne In review [16] [17]	**Peeling , 12 weeks** with erythromycin 2% twice daily with vehicle Absolute results not reported	Reported as not significant P value not reported	⟷	Not significant
[34] RCT	187 people with mild to moderate acne In review [16]	**Adverse effects , 8 weeks** with erythromycin 2% twice daily with vehicle Absolute results not reported Most frequently reported adverse effects were mild burning and peeling	Reported as not significant P value not reported	⟷	Not significant
[36] RCT	253 people with moderate to severe acne In review [16] [17]	**Number of people with one or more adverse effect , 12 weeks** 26 with erythromycin 1.5% twice daily 26 with vehicle Absolute results reported graphically Adverse effects included erythema, scaling, tenderness, and dryness			
[37] RCT	26 people with moderate to severe acne In review [16]	**Adverse effects , 12 weeks** with erythromycin with vehicle RCT reported that "no serious reactions to either formula were observed"			

No data from the following reference on this outcome. [32] [27] [39]

Further information on studies

Comment: Studies of development of bacterial resistance to antibiotics suggest that topical application of antibiotics in acne may result in antibiotic resistance in *Propionibacterium acnes*. [7] [29] One systematic review (search date 2003) analysed the efficacy of topical antibiotics in clinical trials (randomised and non-randomised) conducted between 1966 to 2003 using linear regression. [30] It found that the efficacy of 12 weeks' treatment with topical erythromycin 1.5% to 2% for inflammatory and non-inflammatory lesion count decreased significantly over this period (inflammatory lesions, 8 studies, change in efficacy [regression coefficient]: –2.1%/year, P = 0.001; non-inflammatory lesions, 6 studies, change in efficacy: –2.0%/year, P = 0.001).

Clinical guide:
Topical antibiotics or topical retinoids are indicated as treatment for mild acne that does not respond to benzoyl peroxide. Within the antibiotic class, there is more evidence of benefit with topical erythromycin or clindamycin than with erythromycin plus zinc or tetracycline. However, there is some evidence that topical erythromycin may be less effective now than in the past, owing to increasing *P acnes* resistance.

OPTION TRETINOIN (TOPICAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Topical preparations of tretinoin may reduce inflammatory and non-inflammatory lesions, but can also cause redness, burning, dryness, and soreness of the skin.
- Topical tretinoin has been associated with erythema, peeling, burning, and pruritus.
- Topical retinoids are not recommended in women of childbearing age not taking adequate contraceptive precautions, or during pregnancy.

Benefits and harms

Topical tretinoin versus placebo:

We found one systematic review [16] (search date 1999, 5 RCTs, [40] [41] [42] [43] [44] 802 people with mild to moderate acne, 257 people with moderate to severe acne) comparing topical tretinoin 0.02%, 0.025%, or 0.05% versus vehicle twice daily for 8 to 12 weeks. The review did not perform a meta-analysis because of heterogeneity among the RCTs in methods of outcome assessment. [16]

Acne severity

Topical tretinoin compared with placebo Topical tretinoin may be more effective at 8 to 12 weeks at reducing the number of inflammatory and non-inflammatory lesions in people with mild to severe acne (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Total lesion count					
[43] RCT **3-armed trial**	215 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.025% plus polyol-prepolymer-2	**Percentage reduction in total lesion count , 12 weeks** 40% with tretinoin 0.025% 24% with vehicle Absolute results estimated from graph	P <0.05	○○○	Tretinoin
[44] RCT **3-armed trial**	271 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.025% plus polyol-prepolymer-2	**Percentage reduction in total lesion count , 12 weeks** 39% with tretinoin 0.025% 28% with vehicle Absolute results estimated from graph	P <0.05	○○○	Tretinoin
Non-inflammatory lesions					
[40] RCT **3-armed trial**	256 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.02%	**Comedones (measured by total score) , 7 to 8 weeks** 89 with tretinoin 0.05% 131 with vehicle Completer analysis, no intention-to-treat analysis	P <0.01 for tretinoin 0.05% *v* vehicle The RCT had weak methods for assessing outcomes	○○○	Tretinoin
[40] RCT **3-armed trial**	256 people with mild to moderate acne In review [16]	**Comedones (measured by total score) , 7 to 8 weeks** 94 with tretinoin 0.02% 131 with vehicle	P <0.01 for tretinoin 0.02% *v* vehicle The RCT had weak methods for assessing outcomes	○○○	Tretinoin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm evaluated tretinoin 0.05%	Completer analysis, no intention-to-treat analysis			
[41] RCT **3-armed trial**	257 people with moderate to severe acne In review [16] The remaining arm evaluated motretinide 0.1%	**Number of non-inflammatory lesions , 8 weeks** 89 with tretinoin 0.05% twice daily 131 with vehicle twice daily	P = 0.01	○○○	Tretinoin
[43] RCT **3-armed trial**	215 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.025% plus polyol-prepolymer-2	**Percentage reduction in non-inflammatory lesions , 12 weeks** 39% with tretinoin 0.025% 19% with vehicle Absolute results estimated from graph	P <0.05	○○○	Tretinoin
[44] RCT **3-armed trial**	271 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.025% plus polyol-prepolymer-2	**Percentage reduction in non-inflammatory lesions , 12 weeks** 49% with tretinoin 0.025% 31% with vehicle Absolute results estimated from graph	P <0.05	○○○	Tretinoin
Inflammatory lesions					
[40] RCT **3-armed trial**	256 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.02%	**Number of papules (measured by total score) , 7 to 8 weeks** 61 with tretinoin 0.05% 83 with vehicle Completer analysis, no intention-to-treat analysis	P <0.05 for tretinoin 0.05% *v* vehicle The RCT had weak methods for assessing outcomes	○○○	Tretinoin 0.05%
[40] RCT **3-armed trial**	256 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.05%	**Number of papules (measured by total score) , 7 to 8 weeks** 76 with tretinoin 0.02% 83 with vehicle Completer analysis, no intention-to-treat analysis	Reported as not significant for tretinoin 0.02% *v* vehicle P value not reported The RCT had weak methods for assessing outcomes	⟷	Not significant
[41] RCT **3-armed trial**	257 people with moderate to severe acne In review [16] The remaining arm evaluated motretinide 0.1%	**Number of papules , 8 weeks** 61 with tretinoin 0.05% twice daily 83 with vehicle twice daily	P = 0.05	○○○	Tretinoin
[43] RCT **3-armed trial**	215 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.025% plus polyol-prepolymer-2	**Percentage reduction in papules , 12 weeks** 42% with tretinoin 0.025% 19% with vehicle Absolute results estimated from graph	P <0.05	○○○	Tretinoin

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[44] RCT **3-armed trial**	271 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.025% plus polyol-prepolymer-2	**Percentage reduction in papules , 12 weeks** 49% with tretinoin 0.025% 28% with vehicle Absolute results estimated from graph	P <0.05	○○○	Tretinoin

No data from the following reference on this outcome. [42]

Patient perception of improvement

Topical tretinoin compared with placebo We don't know whether topical tretinoin is more effective at increasing patient perception of improvement in people with mild to moderate acne (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient perception of improvement					
[42] RCT **3-armed trial**	60 people with mild to moderate acne In review [16]	**Patient perception of severity on a visual analogue scale (VAS) , 12 weeks** 18 with tretinoin 0.05% or 0.025% 39 with vehicle Range of VAS not specified	Significance not assessed The RCT had weak methods for assessing outcomes		

Psychological distress

No data from the following reference on this outcome. [40] [41] [42] [43] [44]

Quality of life

No data from the following reference on this outcome. [40] [41] [42] [43] [44]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Erythema					
[40] RCT **3-armed trial**	256 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.02%	**Erythema, peeling, or both , 1 to 3 weeks** 86% with tretinoin 0.05% 40% with vehicle Completer analysis, no intention-to-treat analysis	P <0.01 for tretinoin 0.05% *v* vehicle	○○○	Vehicle
[40] RCT	256 people with mild to moderate acne	**Erythema, peeling, or both , 1 to 3 weeks**	P <0.01 for tretinoin 0.02% *v* vehicle	○○○	Vehicle

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
3-armed trial	In review [16] The remaining arm evaluated tretinoin 0.05%	81% with tretinoin 0.02% 40% with vehicle Completer analysis, no intention-to-treat analysis			
[41] RCT **3-armed trial**	257 people with moderate to severe acne In review [16] The remaining arm evaluated motretinide 0.1%	**Erythema and desquamation , 8 weeks** 76/84 (90%) with tretinoin 0.05% twice daily 16/84 (19%) with vehicle twice daily	P <0.005	○○○	Vehicle
[43] RCT **3-armed trial**	215 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.025% plus polyol-prepolymer-2	**Proportion of people with erythema , 12 weeks** 20% with tretinoin 0.025% 9% with vehicle Absolute results estimated from graph	P <0.005	○○○	Vehicle
[44] RCT **3-armed trial**	271 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.025% plus polyol-prepolymer-2	**Proportion of people with erythema , 12 weeks** 8% with tretinoin 0.025% 3% with vehicle Absolute results estimated from graph	P <0.005	○○○	Vehicle
Burning					
[41] RCT **3-armed trial**	257 people with moderate to severe acne In review [16] The remaining arm evaluated motretinide 0.1%	**Burning , 8 weeks** 69/84 (82%) with tretinoin 0.05% twice daily 23/84 (27%) with vehicle twice daily	P <0.005	○○○	Vehicle
[44] RCT **3-armed trial**	271 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.025% plus polyol-prepolymer-2	**Proportion of people with burning , 12 weeks** 8% with tretinoin 0.025% 3% with vehicle Absolute results estimated from graph	P <0.005	○○○	Vehicle
Itching					
[41] RCT **3-armed trial**	257 people with moderate to severe acne In review [16] The remaining arm evaluated motretinide 0.1%	**Pruritus , 8 weeks** 62/84 (74%) with tretinoin 0.05% twice daily 26/84 (31%) with vehicle twice daily	P <0.005	○○○	Vehicle
[44] RCT **3-armed trial**	271 people with mild to moderate acne In review [16]	**Proportion of people with itching , 12 weeks** 15% with tretinoin 0.025% 6% with vehicle	P <0.005	○○○	Vehicle

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm evaluated tretinoin 0.025% plus polyol-prepolymer-2	Absolute results estimated from graph			
Peeling					
[43] RCT **3-armed trial**	215 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.025% plus polyol-prepolymer-2	**Proportion of people with peeling , 12 weeks** 21% with tretinoin 0.025% 3% with vehicle Absolute results estimated from graph	P <0.005	○○○	Vehicle
Dryness					
[43] RCT **3-armed trial**	215 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.025% plus polyol-prepolymer-2	**Proportion of people with dryness , 12 weeks** 21% with tretinoin 0.025% 8% with vehicle Absolute results estimated from graph	P <0.005	○○○	Vehicle
Skin tightness					
[44] RCT **3-armed trial**	271 people with mild to moderate acne In review [16] The remaining arm evaluated tretinoin 0.025% plus polyol-prepolymer-2	**Proportion of people with skin tightness , 12 weeks** 22% with tretinoin 0.025% 15% with vehicle Absolute results estimated from graph	P <0.005	○○○	Vehicle

Further information on studies

Comment:

Birth defects:
We found no RCTs assessing the risk of birth defects in women using topical retinoids. One non-systematic review found that oral retinoids were teratogenic in case reports and case series in humans, and in experimental studies in animals. [45] In the absence of data regarding the risk of birth defects, it is recommended that topical retinoids are not used during pregnancy, or by women of childbearing age not taking adequate contraceptive precautions. [7]

Clinical guide:
Topical retinoids or topical antibiotics are indicated as treatment for mild acne that does not respond to benzoyl peroxide. Within the retinoid class, there is more evidence of benefit with topical tretinoin than with isotretinoin or adapalene. It is recommended that topical retinoids are not used during pregnancy, or by women of childbearing age not taking adequate contraceptive precautions. [7]

OPTION ADAPALENE (TOPICAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .

- Topical adapalene may reduce inflammatory and non-inflammatory lesions, but can also cause redness, burning, dryness, and soreness of the skin.
- Topical retinoids are not recommended in women of childbearing age not taking adequate contraceptive precautions, or during pregnancy.

Benefits and harms

Topical adapalene versus placebo:

We found one systematic review (search date 2004; 1 RCT) [17] and 3 subsequent RCTs. [46] [47] [48]

Acne severity

Topical adapalene compared with placebo Topical adapalene seems more effective at reducing the number of total lesions and the number of non-inflammatory and inflammatory lesions at 12 weeks in people with mild to moderate acne, and at maintaining improvement of lesions at 16 weeks in people who have responded to previous treatment with oral doxycycline with or without adapalene gel (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Total lesion count					
[49] RCT	237 people with moderate acne In review [17]	**Mean reduction in total lesion count , 12 weeks** 40% with adapalene 0.1% daily 20% with vehicle	P <0.01	○○○	Adapalene
[46] RCT	253 people with severe acne vulgaris who had experienced at least 50% improvement in total lesion count after 12 weeks' treatment with oral doxycycline plus adapalene 0.1% gel or oral doxycycline plus placebo (vehicle)	**Total lesion count , 16 weeks** with adapalene gel 0.1% daily with placebo daily Absolute results reported graphically Maintenance treatment	P = 0.005	○○○	Adapalene
[46] RCT	253 people with severe acne vulgaris who had experienced at least 50% improvement in total lesion count after 12 weeks' treatment with oral doxycycline plus adapalene 0.1% gel or oral doxycycline plus placebo (vehicle)	**Maintenance of at least 50% of the improvement in total lesion count , 16 weeks** 75% with adapalene gel 0.1% daily 54% with placebo daily Absolute numbers not reported Maintenance treatment	P <0.001	○○○	Adapalene
[47] RCT **3-armed trial**	653 people with mild to moderate acne vulgaris The remaining arm evaluated adapalene gel 0.3% daily (258 people)	**Mean reduction in total lesion count , 12 weeks** 48% with adapalene gel 0.1% daily 36% with vehicle daily Absolute numbers not reported	P <0.001 for adapalene 0.1% *v* vehicle	○○○	Adapalene
[47] RCT **3-armed trial**	653 people with mild to moderate acne vulgaris The remaining arm evaluated adapalene gel 0.3% daily (258 people)	**Success rate , 12 weeks** 17% with adapalene gel 0.1% daily 10% with vehicle daily Absolute numbers not reported	P = 0.02 for adapalene 0.1% *v* vehicle	○○○	Adapalene

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		Assessed by the Investigator's Global Assessment (clear or almost clear)			
[47] RCT **3-armed trial**	653 people with mild to moderate acne vulgaris The remaining arm evaluated adapalene gel 0.1% daily (261 people)	**Mean reduction in total lesion count , 12 weeks** 56% with adapalene gel 0.3% daily 36% with vehicle daily Absolute numbers not reported	P value not reported for adapalene 0.3% *v* vehicle		
[47] RCT **3-armed trial**	653 people with mild to moderate acne vulgaris The remaining arm evaluated adapalene gel 0.1% daily (261 people)	**Success rate , 12 weeks** 23% with adapalene gel 0.3% daily 10% with vehicle daily Absolute numbers not reported Assessed by the Investigator's Global Assessment (clear or almost clear)	P value not reported for adapalene 0.3% *v* vehicle		
[48] RCT	200 Japanese people with at least 30 acne lesions	**Median reduction in total lesion count from baseline , 12 weeks** 63.2% with adapalene gel 0.1% daily 36.9% with placebo (vehicle gel) daily Absolute numbers not reported	P <0.0001	○○○	Adapalene
Non-inflammatory lesions					
[49] RCT	237 people with moderate acne In review [17]	**Mean reduction in non-inflammatory lesion count** 38% with adapalene 0.1% daily 20% with vehicle	P <0.01	○○○	Adapalene
[46] RCT	253 people with severe acne vulgaris who had experienced at least 50% improvement in total lesion count after 12 weeks' treatment with oral doxycycline plus adapalene 0.1% gel or oral doxycycline plus placebo (vehicle)	**Non-inflammatory lesion count , 16 weeks** with adapalene gel 0.1% daily with placebo daily Absolute results reported graphically Maintenance treatment	P = 0.02	○○○	Adapalene
[47] RCT **3-armed trial**	653 people with mild to moderate acne vulgaris The remaining arm evaluated adapalene gel 0.3% daily (258 people)	**Mean reduction in non-inflammatory lesions , 12 weeks** 43% with adapalene gel 0.1% daily 29% with vehicle daily Absolute numbers not reported	P <0.001 for adapalene 0.1% *v* vehicle	○○○	Adapalene
[47] RCT **3-armed trial**	653 people with mild to moderate acne vulgaris The remaining arm evaluated adapalene gel 0.1% daily (261 people)	**Mean reduction in non-inflammatory lesion count , 12 weeks** 52% with adapalene gel 0.3% daily 29% with vehicle daily Absolute numbers not reported	P value not reported for adapalene 0.3% *v* vehicle		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[48] RCT	200 Japanese people with at least 30 acne lesions	**Median reduction in number of non-inflammatory lesions from baseline , 12 weeks** 64.6% with adapalene gel 0.1% daily 38.1% with placebo (vehicle gel) daily Absolute numbers not reported	P <0.0001	○○○	Adapalene
Inflammatory lesions					
[49] RCT	237 people with moderate acne In review [17]	**Mean reduction in inflammatory lesion count** 35% with adapalene 0.1% daily 19% with vehicle	P <0.01	○○○	Adapalene
[46] RCT	253 people with severe acne vulgaris who had experienced at least 50% improvement in total lesion count after 12 weeks' treatment with oral doxycycline plus adapalene 0.1% gel or oral doxycycline plus placebo (vehicle)	**Inflammatory lesion count , 16 weeks** with adapalene gel 0.1% daily with placebo daily Absolute results reported graphically Maintenance treatment	P = 0.01	○○○	Adapalene
[47] RCT **3-armed trial**	653 people with mild to moderate acne vulgaris The remaining arm evaluated adapalene gel 0.3% daily (258 people)	**Mean reduction in inflammatory lesions , 12 weeks** 58% with adapalene gel 0.1% daily 47% with vehicle daily Absolute numbers not reported	P <0.001 for adapalene 0.1% *v* vehicle	○○○	Adapalene
[47] RCT **3-armed trial**	653 people with mild to moderate acne vulgaris The remaining arm evaluated adapalene gel 0.1% daily (261 people)	**Mean reduction in inflammatory lesions , 12 weeks** 63% with adapalene gel 0.3% daily 47% with vehicle daily Absolute numbers not reported	P value not reported for adapalene 0.1% *v* vehicle		
[48] RCT	200 Japanese people with at least 30 acne lesions	**Median reduction in number of inflammatory lesions from baseline , 12 weeks** 63.7% with adapalene gel 0.1% daily 45.8% with placebo (vehicle gel) daily Absolute numbers not reported	P = 0.001	○○○	Adapalene

Patient perception of improvement

Topical adapalene compared with placebo We don't know whether topical adapalene is more effective at improving patient satisfaction in people with acne (at least 30 lesions) at 12 weeks, but topical adapalene may be more effective at increasing patient satisfaction with maintenance treatment at 12 weeks in people with severe acne who have responded to previous treatment with oral doxycycline with or without adapalene gel (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient perception of improvement					
[46] RCT	253 people with severe acne vulgaris who had experienced at least 50% improvement in total lesion count after 12 weeks' treatment with oral doxycycline plus adapalene 0.1% gel or oral doxycycline plus placebo (vehicle)	**Proportion reporting being "satisfied" or "very satisfied" with maintenance treatment , 12 weeks** 76% with adapalene gel 0.1% daily 65% with placebo daily Absolute numbers not reported Maintenance treatment Details of satisfaction scale not reported	P = 0.01	○○○	Adapalene
[48] RCT	200 Japanese people with at least 30 acne lesions	**Proportion of people with greater than 75% satisfaction with treatment effect on a visual analogue scale (VAS) , 12 weeks** 60% with adapalene gel 0.1% daily 42% with placebo (vehicle gel) daily Absolute numbers not reported VAS scale of 0 to 100, where 0 = entirely unsatisfied, 100 = fully satisfied			

Quality of life

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Quality of life					
[49] RCT	237 people with moderate acne In review [17]	**Quality of life , 12 weeks** with adapalene 0.1% daily with vehicle Absolute results not reported Assessed through a patient questionnaire that evaluated self-perception, social and emotional status, and acne symptoms. The RCT found similar scores in both groups			

No data from the following reference on this outcome. [46] [47]

Psychological distress

No data from the following reference on this outcome. [46] [47] [49]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Skin adverse effects					
[49] RCT	237 people with moderate acne In review [17]	**Adverse effects (erythema, dryness, scaling, stinging/burning, and pruritus) , 2 weeks** with adapalene 0.1% daily with vehicle Highest incidence of adverse effects occurred at 2 weeks 2 people taking adapalene withdrew, one because of adverse effects	P <0.01	○○○	Vehicle
[49] RCT	237 people with moderate acne In review [17]	**Adverse effects (erythema, dryness, scaling, stinging/burning) , 12 weeks** with adapalene 0.1% daily with vehicle 2 people taking adapalene withdrew, one because of adverse effects	Reported as not significant P value not reported	⟷	Not significant
[46] RCT	253 people with severe acne vulgaris who had experienced at least 50% improvement in total lesion count after 12 weeks' treatment with oral doxycycline plus adapalene 0.1% gel or oral doxycycline plus placebo (vehicle)	**Adverse effects (erythema, scaling, dryness, stinging, burning)** 25% with adapalene gel 0.1% daily 23% with placebo daily Absolute numbers not reported Maintenance treatment	Significance not assessed		
[47] RCT **3-armed trial**	653 people with mild to moderate acne vulgaris The remaining arm evaluated adapalene gel 0.3% daily (258 people)	**Adverse effects (dry skin and skin discomfort) , 12 weeks** 22% with adapalene gel 0.3% daily 12% with adapalene gel 0.1% daily 5% with vehicle daily Absolute numbers not reported	Significance not assessed		
[48] RCT	200 Japanese people with at least 30 acne lesions	**Adverse events related to study drugs , 12 weeks** 56/100 (56%) with adapalene gel 0.1% daily 8/99 (8%) with placebo (vehicle gel) daily These were dermatological in nature and the most common was dry skin			

Further information on studies

Comment:

Birth defects:
We found no RCTs assessing the risk of birth defects in women using topical retinoids. One non-systematic review found that oral retinoids were teratogenic in case reports and case series in humans, and in experimental studies in animals. [45] In the absence of data regarding the risk of birth defects, it is recommended that topical retinoids are not used during pregnancy, or by women of childbearing age not taking adequate contraceptive precautions. [7]

Clinical guide:
Topical retinoids or topical antibiotics are indicated as treatment for mild acne that does not respond to benzoyl peroxide. Within the retinoid class, there is more evidence of benefit with topical tretinoin than with isotretinoin or adapalene. It is recommended that topical retinoids are not used during pregnancy, or by women of childbearing age not taking adequate contraceptive precautions. [7] Adapalene 0.3% is not available in the UK.

OPTION AZELAIC ACID (TOPICAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Topical azelaic acid reduces inflammatory and non-inflammatory lesions compared with placebo, but can cause itching, burning, stinging, and redness of the skin.
- Topical azelaic acid has been associated with itching, stinging, burning, and erythema.

Benefits and harms

Azelaic acid versus placebo:

We found two systematic reviews, which compared topical azelaic acid 20% versus placebo. [16] [17] The first review (search date 1999) [16] identified two RCTs. [50] [51] The second review (search date 2004), [17] which had more stringent inclusion criteria than the earlier review, included one RCT [51] also identified by the earlier review.

Acne severity

Azelaic acid compared with placebo Topical azelaic acid may be more effective at 8 to 12 weeks at reducing the number of comedones and inflammatory lesions in people with moderate acne (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Total lesion count					
[51] RCT	92 people with moderate acne In review [16] [17]	**Proportion of people who had a physician rating of response to treatment of "excellent" or "good" , 12 weeks** 28/43 (65%) with azelaic acid 18/49 (37%) with placebo Reduction in total lesion count by 75% to 100% rated as "excellent" and 50% to 75% as "good"	P = 0.05	○○○	Azelaic acid
Non-inflammatory lesions					
[51] RCT	92 people with moderate acne In review [16] [17]	**Percentage reduction in comedones** 56% with azelaic acid 0% with placebo 13% of people did not complete the trial; no intention-to-treat analysis	P = 0.05	○○○	Azelaic acid
[50] RCT	40 people, severity of acne unclear In review [16] Unclear whether people taking azelaic acid and placebo had comparable duration	**Percentage reduction in non-inflammatory lesions , 8 weeks** 50% with azelaic acid 25% with placebo	P = 0.027	○○○	Azelaic acid

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	and severity of acne				
Inflammatory lesions					
[51] RCT	92 people with moderate acne In review [16] [17]	**Percentage reduction in inflammatory lesions** 72% with azelaic acid 47% with vehicle 13% of people did not complete the trial; no intention-to-treat analysis	P = 0.05	○○○	Azelaic acid
[50] RCT	40 people, severity of acne unclear In review [16] Unclear whether people taking azelaic acid and placebo had comparable duration and severity of acne	**Percentage reduction in inflammatory lesions , 8 weeks** 50% with azelaic acid 12% with placebo	P = 0.001	○○○	Azelaic acid

Patient perception of improvement

No data from the following reference on this outcome. [50] [51]

Psychological distress

No data from the following reference on this outcome. [50] [51]

Quality of life

No data from the following reference on this outcome. [50] [51]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[51] RCT	92 people with moderate acne In review [16] [17]	**Proportion of people with burning** 4/43 (9%) with azelaic acid 1/49 (2%) with vehicle	Significance not assessed		
[51] RCT	92 people with moderate acne In review [16] [17]	**Proportion of people with itching** 2/43 (5%) with azelaic acid	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		0/49 (0%) with vehicle			
[51] RCT	92 people with moderate acne In review [16] [17]	**Proportion of people with erythema** 2/43 (5%) with azelaic acid 1/49 (2%) with vehicle	Significance not assessed		
[50] RCT	40 people, severity of acne unclear In review [16] Unclear whether people taking azelaic acid and placebo had comparable duration and severity of acne	**Itching and stinging , 8 weeks** 2/20 (10%) with azelaic acid 1/20 (5%) with placebo	Significance not assessed		

Further information on studies

Comment: One non-systematic review of RCTs and uncontrolled studies found that 0% to 5% of people taking azelaic acid had scaling, 5% to 23% had burning, and 13% to 29% had itching. [52]

Clinical guide:
Azelaic acid is a similar type of treatment to benzoyl peroxide, but there is less evidence of benefit for azelaic acid than for benzoyl peroxide. It can also cause irritation, which is helped by reducing the frequency of application or temporarily discontinuing treatment.

OPTION ERYTHROMYCIN PLUS ZINC (TOPICAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Topical antibiotics, such as erythromycin with zinc, reduce inflammatory lesions compared with placebo, but have not been shown to reduce non-inflammatory lesions.

Benefits and harms

Topical erythromycin plus zinc versus placebo:

We found one systematic review (search date 1999, 2 RCTs, 222 people with mild to severe acne), which compared topical erythromycin 4% plus zinc acetate 1.2% versus placebo. [16] The review did not perform a meta-analysis because of heterogeneity among the trials in outcomes assessed.

Acne severity

Topical erythromycin plus zinc compared with placebo Topical erythromycin plus zinc may be more effective at reducing inflammatory and non-inflammatory lesions and at reducing overall acne severity at 10 to 12 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall severity					
[53] RCT	149 men, severity of acne unclear In review [16]	**Reduction in severity measured by Cook's acne grading scale , 10 weeks**	P <0.001 for topical erythromycin plus zinc liquid plus oral placebo *v* topical vehicle plus oral placebo	○○○	Erythromycin plus zinc

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
4-armed trial	The remaining arms evaluated oral tetracycline 250 mg twice daily plus topical vehicle and topical erythromycin (4%) plus zinc acetate (1.2%) gel plus oral placebo	46% with topical erythromycin (4%) plus zinc octoate (1.2%) liquid plus oral placebo 7% with topical vehicle plus oral placebo			
[53] RCT **4-armed trial**	149 men, severity of acne unclear In review [16] The remaining arms evaluated oral tetracycline 250 mg twice daily plus topical vehicle and topical erythromycin (4%) plus zinc octoate (1.2%) liquid plus oral placebo	**Reduction in severity measured by Cook's acne grading scale , 10 weeks** 33% with topical erythromycin (4%) plus zinc acetate (1.2%) gel plus oral placebo 7% with topical vehicle plus oral placebo	P <0.01 for topical erythromycin plus zinc gel plus oral placebo *v* topical vehicle plus oral placebo	○○○	Erythromycin plus zinc
Non-inflammatory lesions					
[54] RCT	73 women with Cook's acne grade score 3 or more In review [16]	**Reduction in non-inflammatory lesions , 12 weeks** 61% with topical erythromycin plus zinc acetate 48% with vehicle	P <0.01	○○○	Erythromycin plus zinc
Inflammatory lesions					
[53] RCT **4-armed trial**	149 men, severity of acne unclear In review [16] The remaining arms evaluated oral tetracycline 250 mg twice daily plus topical vehicle and topical erythromycin (4%) plus zinc acetate (1.2%) gel plus oral placebo	**Reduction in papules measured by Cook's acne grading scale , 10 weeks** 58% with topical erythromycin (4%) plus zinc octoate (1.2%) liquid plus oral placebo 25% with topical vehicle plus oral placebo	P <0.001 for topical erythromycin plus zinc liquid plus oral placebo *v* topical vehicle plus oral placebo	○○○	Erythromycin plus zinc
[53] RCT **4-armed trial**	149 men, severity of acne unclear In review [16] The remaining arms evaluated oral tetracycline 250 mg twice daily plus topical vehicle and topical erythromycin (4%) plus zinc octoate (1.2%) liquid plus oral placebo	**Reduction in papules measured by Cook's acne grading scale , 10 weeks** 45% with topical erythromycin (4%) plus zinc acetate (1.2%) gel plus oral placebo 25% with topical vehicle plus oral placebo	P <0.05 for topical erythromycin plus zinc gel plus oral placebo *v* topical vehicle plus oral placebo	○○○	Erythromycin plus zinc

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[53] RCT **4-armed trial**	149 men, severity of acne unclear In review [16] The remaining arms evaluated oral tetracycline 250 mg twice daily plus topical vehicle and topical erythromycin (4%) plus zinc acetate (1.2%) gel plus oral placebo	**Reduction in pustules measured by Cook's acne grading scale , 10 weeks** with topical erythromycin (4%) plus zinc octoate (1.2%) liquid plus oral placebo with topical vehicle plus oral placebo Absolute results not reported	Reported as not significant for topical erythromycin plus zinc liquid plus oral placebo *v* topical vehicle plus oral placebo P value not reported	⟷	Not significant
[53] RCT **4-armed trial**	149 men, severity of acne unclear In review [16] The remaining arms evaluated oral tetracycline 250 mg twice daily plus topical vehicle and topical erythromycin (4%) plus zinc octoate (1.2%) liquid plus oral placebo	**Reduction in pustules measured by Cook's acne grading scale , 10 weeks** with topical erythromycin (4%) plus zinc acetate (1.2%) gel plus oral placebo with topical vehicle plus oral placebo Absolute results not reported	Reported as not significant for topical erythromycin plus zinc gel plus oral placebo *v* topical vehicle plus oral placebo P value not reported	⟷	Not significant
[54] RCT	73 women with Cook's acne grade score 3 or more In review [16]	**Reduction in inflammatory lesions , 12 weeks** 73% with topical erythromycin (4%) plus zinc acetate (1.2%) twice daily 46% with vehicle	P <0.01	○○○	Erythromycin plus zinc

Patient perception of improvement

No data from the following reference on this outcome. [53] [54]

Psychological distress

No data from the following reference on this outcome. [53] [54]

Quality of life

No data from the following reference on this outcome. [53] [54]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[53] RCT **4-armed trial**	149 men, severity of acne unclear In review [16] The remaining arm evaluated oral tetracycline 250 mg twice daily plus topical vehicle	**Adverse effects , 10 weeks** with topical erythromycin (4%) plus zinc octoate (1.2%) liquid plus oral placebo with topical erythromycin (4%) plus zinc acetate (1.2%) gel plus oral placebo with topical vehicle plus oral placebo One person withdrew because of irritation with topical erythromycin plus zinc acetate plus oral placebo			
[54] RCT	73 women with Cook's acne grade score 3 or more In review [16]	**Adverse effects , 12 weeks** with topical erythromycin plus zinc acetate with vehicle The RCT reported that no one withdrew from the trial owing to irritation or other adverse effects of treatment			

Further information on studies

Comment: Studies of development of bacterial resistance to antibiotics suggest that topical application of antibiotics in acne may result in antibiotic resistance in *Propionibacterium acnes*. [7] [29] One systematic review (search date 2003) has found evidence that the efficacy of topical erythromycin 1.5% to 2% has decreased over the period 1966 to 2003, which may be as a result of increasing bacterial resistance (see comment on topical erythromycin, p 12). [30]

Clinical guide:
Topical antibiotics or topical retinoids are indicated as treatment for mild acne that does not respond to benzoyl peroxide. Within the antibiotic class, there is more evidence of benefit with topical clindamycin or erythromycin than with erythromycin plus zinc or tetracycline. However, there is some evidence that topical erythromycin may be less effective now than in the past, owing to increasing *P acnes* resistance. Erythromycin plus zinc is available as a formulated combination topical solution.

OPTION ISOTRETINOIN (TOPICAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Topical preparations of isotretinoin may reduce inflammatory and non-inflammatory lesions, but can also cause redness, burning, dryness, and soreness of the skin.
- Topical isotretinoin has been associated with severe erythema, dryness, soreness, and burning.
- Topical retinoids are not recommended in women of childbearing age who are not taking adequate contraceptive precautions, or during pregnancy.

Benefits and harms

Topical isotretinoin versus placebo:

We found one systematic review [16] (search date 1999, 3 RCTs, [20] [55] [56] 472 people with mild to moderate acne) and one subsequent RCT [32] comparing isotretinoin versus placebo (vehicle). The review did not perform a meta-analysis because of heterogeneity among the trials in methods of outcome assessment. [16]

Acne severity

Topical isotretinoin compared with placebo Topical isotretinoin may be more effective at reducing the number of inflammatory and non-inflammatory lesions at 12 weeks in people with mild to moderate acne (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall severity					
[55] RCT	313 people with moderate acne In review [16]	**Mean reduction in severity scores** 40% with isotretinoin 20% with vehicle Measured by Cook's acne grading scale method [14]	Reported as significant P value not reported	◌◌◌	Isotretinoin
[20] RCT **3-armed trial**	77 people with mild to moderate acne In review [16] The remaining arm evaluated benzoyl peroxide	**Mean change in severity scores , 12 weeks** 0 with isotretinoin 1 with vehicle Measured using the Leeds score where 0 = no acne and 10 = severest acne	P <0.05 for isotretinoin *v* vehicle	◌◌◌	Isotretinoin
[32] RCT **4-armed trial**	160 people with mild to moderate acne The remaining arms evaluated erythromycin 2% alone and isotretinoin plus erythromycin	**Mean change in total lesion count from baseline , 12 weeks** –21.52% (95% CI –32.44% to –10.60%) with isotretinoin –10.82% (95% CI –24.29% to +2.65% with vehicle	Significance of between-group difference not assessed		
Non-inflammatory lesions					
[55] RCT	313 people with moderate acne In review [16]	**Mean reduction in non-inflammatory lesions** 46% with isotretinoin 14% with vehicle	Reported as significant P value not reported	◌◌◌	Isotretinoin
[20] RCT **3-armed trial**	77 people with mild to moderate acne In review [16] The remaining arm evaluated benzoyl peroxide	**Mean change in number of non-inflammatory lesions , 12 weeks** –47% with isotretinoin +6% with vehicle	P = 0.01 for isotretinoin *v* vehicle	◌◌◌	Isotretinoin
[32] RCT **4-armed trial**	160 people with mild to moderate acne The remaining arms evaluated erythromycin 2% alone and isotretinoin plus erythromycin	**Mean change in non-inflammatory lesion count from baseline , 12 weeks** –18.49 (95% CI –35.5 to –1.63) with isotretinoin –7.07 (95% CI –28.31 to +14.16) with vehicle	Significance of between-group difference not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Inflammatory lesions					
[55] RCT	313 people with moderate acne In review [16]	**Mean reduction in inflammatory lesions** 55% with isotretinoin 25% with vehicle	Reported as significant P value not reported	○○○	Isotretinoin
[20] RCT **3-armed trial**	77 people with mild to moderate acne In review [16] The remaining arm evaluated benzoyl peroxide	**Mean change in number of inflammatory lesions , 12 weeks** –33% with isotretinoin +9% with vehicle	P = 0.01 for isotretinoin *v* vehicle	○○○	Isotretinoin
[56] RCT **3-armed trial**	82 people with mild to moderate acne In review [16]	**Mean change in papules from baseline , 12 weeks** –7.6 with isotretinoin 0.05% –13.3 with isotretinoin 0.1% –7.3 with placebo	Significance of differences between groups not assessed		
[56] RCT **3-armed trial**	82 people with mild to moderate acne In review [16]	**Mean change in whiteheads from baseline , 12 weeks** –9.6 with isotretinoin 0.05% –9.4 with isotretinoin 0.1% –2.6 with placebo	Significance of differences between groups not assessed		
[32] RCT **4-armed trial**	160 people with mild to moderate acne The remaining arms evaluated erythromycin 2% alone and isotretinoin plus erythromycin	**Mean change in inflammatory lesion count from baseline , 12 weeks** –15.66 (95% CI –27.71 to –3.62) with isotretinoin –9.58 (95% CI –24.51 to +5.36) with vehicle	Significance of differences between groups not assessed		

Patient perception of improvement

Topical isotretinoin compared with placebo We don't know whether topical isotretinoin is more effective at increasing the proportion of people who perceive their acne as improved at 12 weeks (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient perception of improvement					
[32] RCT **4-armed trial**	160 people with mild to moderate acne The remaining arms evaluated erythromycin 2% alone and isotretinoin plus erythromycin	**Proportion of people who perceived that their acne had improved from baseline , 12 weeks** 66% with isotretinoin 53% with vehicle Absolute numbers not reported	Significance not assessed		

Psychological distress

No data from the following reference on this outcome. [20] [55] [56] [32]

Quality of life

No data from the following reference on this outcome. [20] [55] [56] [32]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Skin adverse effects					
[55] RCT	313 people with moderate acne In review [16]	**Proportion of people with peeling** 71% with isotretinoin 51% with vehicle Absolute numbers not reported	Significance not assessed		
[55] RCT	313 people with moderate acne In review [16]	**Proportion of people with erythema** 76% with isotretinoin 62% with vehicle Absolute numbers not reported	Significance not assessed		
[20] RCT **3-armed trial**	77 people with mild to moderate acne In review [16] The remaining arm evaluated benzoyl peroxide	**Adverse effects , 12 weeks** with isotretinoin with vehicle The RCT found that isotretinoin was associated with severe erythema (2 people), dryness (3 people), redness (10 people), soreness (4 people), and burning (4 people). One person taking isotretinoin withdrew because of erythema			
[56] RCT **3-armed trial**	82 people with mild to moderate acne In review [16]	**Peeling , 12 weeks** with isotretinoin 0.05% with isotretinoin 0.1% with placebo Absolute results not reported The RCT found that isotretinoin (0.05% and 0.1%) significantly increased peeling	P <0.01 Unclear whether P value is for separate comparisons of isotretinoin *v* placebo or combined analysis of both isotretinoin groups versus placebo		
[32] RCT **4-armed trial**	160 people with mild to moderate acne The remaining arms evaluated erythromycin 2% alone and isotretinoin plus erythromycin	**Overall tolerance , 12 weeks** with isotretinoin with vehicle	Reported as not significant P value not reported This RCT is likely to have been underpowered to detect a clinically important difference in adverse effects among treatments		

Further information on studies

Comment:

Birth defects:
In the absence of data regarding the risk of birth defects, it is recommended that topical retinoids are not used during pregnancy, or by women of childbearing age not taking adequate contraceptive precautions. [7]

Clinical guide:
Topical retinoids or topical antibiotics are indicated as treatment for mild acne that does not respond to benzoyl peroxide. Within the retinoid class, there is more evidence of benefit with topical tretinoin than with isotretinoin or adapalene. It is recommended that topical retinoids are not used during pregnancy, or by women of childbearing age who are not taking adequate contraceptive precautions. [7]

OPTION TETRACYCLINE (TOPICAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Tetracycline may reduce overall acne severity.
- Antimicrobial resistance can develop with use of topical or oral antibiotics, and their efficacy may decrease over time.
- Tetracyclines may cause skin discoloration, and should be avoided in pregnant or breastfeeding women.

Benefits and harms

Topical tetracycline versus placebo:

We found one systematic review (search date 1999, 4 RCTs, 355 people with moderate to severe acne). [16] The review did not perform a meta-analysis because of heterogeneity among the trials in outcomes assessed.

Acne severity

Topical tetracycline compared with placebo Topical tetracycline may be more effective at reducing severity of acne at 12 to 16 weeks in people with mild to moderate acne (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall severity					
[57] RCT **3-armed trial**	75 people In review [16] The remaining arm evaluated oral tetracycline 250 mg twice daily plus topical placebo	**Mean reduction in severity , 12 weeks** 1.43 with topical tetracycline 0.5% plus oral placebo 0.62 with topical plus oral placebo Measured by Cook's acne grading scale [14] 11/75 (15%) people withdrew from the trial, no intention-to-treat analysis of results	P <0.05	○○○	Tetracycline
[58] RCT **3-armed trial**	60 male adolescents In review [16] The remaining arm evaluated topical vehicle plus oral tetracycline	**Proportion of people with improvement of at least 1 on a scale from 0 (least improvement) to 8 (most improvement)** 14/19 (74%) with topical tetracycline plus oral placebo 6/17 (35%) with topical vehicle plus oral placebo	Significance not assessed		
[59] RCT **3-armed trial**	135 people aged 18 to 25 years with mild to moderate acne In review [16]	**Acne severity , 7, 10, and 12 weeks** with topical tetracycline 0.22% plus oral placebo with topical vehicle plus oral placebo	P <0.05	○○○	Tetracycline

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	The remaining arm evaluated oral tetracycline plus topical vehicle	Absolute results reported graphically Measured using Cook's acne grades 0 to 8			
[60] RCT	85 people with mild to moderate acne In review [16]	**Proportion of people who had improved acne on a scale from 0 to 8 , 16 weeks** 29/31 (94%) with topical tetracycline 2.2% 13/23 (57%) with placebo Unclear how the authors dichotomised results to calculate the proportion of people who had improved acne severity All participants took oral tetracycline for 8 weeks before beginning treatment with topical tetracycline or placebo	P = 0.035	○○○	Tetracycline

Patient perception of improvement

Topical tetracycline compared with placebo Topical tetracycline may be no more effective at increasing the proportion of people who consider their condition better than before treatment (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient perception of improvement					
[60] RCT	85 people with mild to moderate acne In review [16]	**Proportion of people who considered that their condition was better than before treatment** 25/31 (81%) with topical tetracycline 18/24 (75%) with placebo All participants took oral tetracycline for 8 weeks before beginning treatment with topical tetracycline or placebo	Significance not assessed		

No data from the following reference on this outcome. [57] [58] [59]

Psychological distress

No data from the following reference on this outcome. [57] [58] [59] [60]

Quality of life

No data from the following reference on this outcome. [57] [58] [59] [60]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Skin discoloration					
[57] RCT **3-armed trial**	75 people In review [16] The remaining arm evaluated oral tetracycline 250 mg twice daily plus topical placebo	**Skin discoloration** with topical tetracycline 0.5% plus oral placebo with topical plus oral placebo The RCT found that some people using topical tetracycline had skin discoloration 11/75 (15%) people withdrew from the trial, no intention-to-treat analysis of results			
[59] RCT **3-armed trial**	135 people aged 18 to 25 years with mild to moderate acne In review [16] The remaining arm evaluated oral tetracycline plus topical vehicle	**Skin discoloration** with topical tetracycline 0.22% plus oral placebo with topical vehicle plus oral placebo Absolute results reported graphically The RCT found that some people using topical tetracycline had skin discoloration			
[60] RCT	85 people with mild to moderate acne In review [16]	**Proportion of people with skin discoloration** 17/43 (40%) with topical tetracycline 2.2% 4/42 (10%) with placebo All participants took oral tetracycline for 8 weeks before beginning treatment with topical tetracycline or placebo	P <0.005	○○○	Placebo

No data from the following reference on this outcome. [58]

Further information on studies

Comment: Studies of development of bacterial resistance to antibiotics suggest that topical application of antibiotics in acne may result in antibiotic resistance in *Propionibacterium acnes*. [7] [29]

Clinical guide:
Topical antibiotics or topical retinoids are indicated as treatment for mild acne that does not respond to benzoyl peroxide. Within the antibiotic class, there is more evidence of benefit with topical clindamycin or erythromycin than with erythromycin plus zinc, or with tetracycline.

QUESTION What are the effects of oral treatments in people with acne vulgaris?

OPTION ERYTHROMYCIN (ORAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Oral erythromycin is considered useful for people with more severe acne, although we don't know for sure whether it is effective. Oral antibiotics can cause adverse effects such as contraceptive failure.

Benefits and harms

Oral erythromycin versus placebo:

We found two systematic reviews (search dates 2004; [17] not reported [61]), which identified no RCTs comparing oral erythromycin versus placebo. We found no subsequent RCTs.

Oral erythromycin versus oral doxycycline:

We found one RCT. [62]

Acne severity

Oral erythromycin compared with oral doxycycline We don't know how oral erythromycin and oral doxycycline compare at reducing the number of papules and pustules at 6 weeks in people with moderate acne (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Inflammatory lesions					
[62] RCT	56 people with moderate acne Before treatment, people taking doxycycline had a mean of 38 inflammatory lesions, and people taking erythromycin had a mean of 46 inflammatory lesions (significance not assessed)	**Mean number of papules and pustules , 6 weeks** 16 with oral doxycycline (100 mg daily for 2 weeks, then on alternate days for 4 weeks) 15 with oral erythromycin (500 mg twice daily for 2 weeks, then 250 mg twice daily for 4 weeks)	P >0.1	⟷	Not significant

Patient perception of improvement

No data from the following reference on this outcome. [62]

Psychological distress

No data from the following reference on this outcome. [62]

Quality of life

No data from the following reference on this outcome. [62]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[62] RCT	56 people with moderate acne	**Adverse effects , 6 weeks**			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	Before treatment, people taking doxycycline had a mean of 38 inflammatory lesions, and people taking erythromycin had a mean of 46 inflammatory lesions (significance not assessed)	with doxycycline (100 mg daily for 2 weeks, then on alternate days for 4 weeks) with erythromycin (500 mg twice daily for 2 weeks, then 250 mg twice daily for 4 weeks) The RCT reported no withdrawals due to adverse effects, but gave no further information			

Oral erythromycin versus oral tetracycline:

We found two systematic reviews. [16] [17] The first review (search date 1999) [16] identified 3 RCTs (300 people) [63] [64] [65], which compared oral erythromycin versus oral tetracycline in people with mild, moderate, or severe acne. The second review (search date 2004), [17] which had more stringent inclusion criteria, included one RCT identified by the first review. [64]

Acne severity

Oral erythromycin compared with oral tetracycline We don't know how oral erythromycin and oral tetracycline compare at improving inflammation scores at 6 months, or at reducing the number of pustules, papules, or open or closed comedones at 12 weeks in people with moderate to severe acne (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall severity					
[63] RCT	60 people with moderate to severe acne In review [16]	**Proportion of people symptom-free , 6 months** 9/21 (43%) with erythromycin 200 to 400 mg daily 7/21 (33%) with tetracycline 250 to 400 mg daily	Reported as not significant P value not reported	⟷	Not significant
[65] RCT	40 people with mild, moderate, or severe acne In review [16]	**Proportion with "good" or "very good" response as assessed by their physician , 16 weeks** 65% with erythromycin 250 mg twice daily 90% with tetracycline 250 mg twice daily	Significance not assessed		
Non-inflammatory lesions					
[64] RCT	200 people with moderate to severe acne In review [16] [17]	**Percentage change in open comedones , 12 weeks** –26% with erythromycin (333 mg 3 times daily for 4 weeks, then once daily for 8 weeks) –31% with tetracycline (500 mg twice daily for 4 weeks, then once daily for 8 weeks)	Reported as not significant P value not reported	⟷	Not significant
[64] RCT	200 people with moderate to severe acne In review [16] [17]	**Percentage change in closed comedones , 12 weeks** –17% with erythromycin (333 mg 3 times daily for 4 weeks, then once daily for 8 weeks)	Reported as not significant P value not reported	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		–36% with tetracycline (500 mg twice daily for 4 weeks, then once daily for 8 weeks)			
Inflammatory lesions					
[63] RCT	60 people with moderate to severe acne In review [16]	**Inflammation score on face , 6 months** 1 with erythromycin 200 to 400 mg daily 1 with tetracycline 250 to 400 mg daily	Reported as not significant P value not reported	⟷	Not significant
[64] RCT	200 people with moderate to severe acne In review [16] [17]	**Percentage change in papules , 12 weeks** –60% with erythromycin (333 mg 3 times daily for 4 weeks, then once daily for 8 weeks) –62% with tetracycline (500 mg twice daily for 4 weeks, then once daily for 8 weeks)	Reported as not significant P value not reported	⟷	Not significant
[64] RCT	200 people with moderate to severe acne In review [16] [17]	**Percentage change in pustules , 12 weeks** –73% with erythromycin (333 mg 3 times daily for 4 weeks, then once daily for 8 weeks) –65% with tetracycline (500 mg twice daily for 4 weeks, then once daily for 8 weeks)	Reported as not significant P value not reported	⟷	Not significant

Patient perception of improvement

Oral erythromycin compared with oral tetracycline Oral erythromycin and oral tetracycline are equally effective at increasing the proportion of people with moderate to severe acne who perceive their acne as markedly improved or improved at 12 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient perception of improvement					
[64] RCT	200 people with moderate to severe acne In review [16] [17]	**Proportion of people who reported acne as "markedly improved" or "improved" , 12 weeks** 77% with erythromycin (333 mg 3 times daily for 4 weeks, then once daily for 8 weeks) 89% with tetracycline (500 mg twice daily for 4 weeks, then once daily for 8 weeks)	Reported as not significant P value not reported	⟷	Not significant

No data from the following reference on this outcome. [63] [65]

Psychological distress

No data from the following reference on this outcome. [63] [64] [65]

Quality of life

No data from the following reference on this outcome. [63] [64] [65]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[63] RCT	60 people with moderate to severe acne In review [16]	**Adverse effects** with erythromycin 200 to 400 mg daily with tetracycline 250 to 400 mg daily One person in each treatment group discontinued treatment in the first week because of diarrhoea, and 14% of people in the trial had adverse effects, mostly gastrointestinal			
[64] RCT	200 people with moderate to severe acne In review [16] [17]	**Number of people reporting an adverse effect** 12 with erythromycin (333 mg 3 times daily for 4 weeks, then once daily for 8 weeks) 7 with tetracycline (500 mg twice daily for 4 weeks, then once daily for 8 weeks) Adverse effects were mostly gastrointestinal One person taking oral tetracycline developed a pseudotumour cerebri, but later recovered			
[65] RCT	40 people with mild, moderate, or severe acne In review [16]	**Adverse effects** with erythromycin 250 mg twice daily with tetracycline 250 mg twice daily One person taking erythromycin had nausea and vomiting, and one person taking tetracycline had mild diarrhoea, one had nausea, and one had pruritus			

Further information on studies

Comment: *Propionibacterium acnes* is becoming increasingly resistant to systemic antibiotics. One systematic review (search date 1998, 12 studies) found an increase in the prevalence of *P acnes* resistance from 20% in 1978 to 62% in 1996. [66] Resistance to systemic antibiotics varied, but was most commonly reported in people taking erythromycin, clindamycin, tetracycline, doxycycline, and trimethoprim. Resistance to minocycline was rare.

Clinical guide:
Oral antibiotics are indicated as treatment for moderate acne that does not respond to topical treatments, and can be supplemented by non-antibiotic topical treatment (e.g., benzoyl peroxide) if needed. There is evidence that erythromycin is effective, but there are some concerns about bacterial resistance. Oral antibiotics may cause failure of oral contraceptives during the initial weeks of treatment.

OPTION DOXYCYCLINE (ORAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Oral doxycycline is considered useful for people with more severe acne, although we don't know for sure whether it is effective.
- Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. They may cause contraceptive failure during the initial weeks of treatment.

Benefits and harms

Oral doxycycline versus placebo:

We found 3 systematic reviews (search dates 1999, [16] 2004, [17] not reported [61]), which between them identified two RCTs comparing doxycycline versus placebo. [67] [68]

Acne severity

Oral doxycycline compared with placebo Oral doxycycline may be more effective than placebo at improving clinician's global assessment and inflammatory and non-inflammatory lesions after 6 months in people with moderate acne. However, we don't know whether oral doxycycline is more effective at reducing the number of inflammatory lesions at 4 weeks in people with mild acne (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Total lesion count					
[68] RCT	51 people with moderate acne In review [17] [61]	**Clinician's global assessment scores , 6 months** 4.4 with doxycycline 20 mg twice daily 5.1 with placebo Measured on a scale from 1 to 7 where 1 = clear or almost clear skin	P = 0.03	○○○	Doxycycline
Inflammatory lesions					
[67] RCT **Crossover design**	62 people with mild acne In review [16] [61]	**Percentage change in the number of inflammatory lesions from baseline , 4 weeks** –36% with oral doxycycline 100 mg daily +12% with placebo Pre-crossover results Oral doxycycline significantly improved lesion count from baseline (P = 0.0001)	Significance of between-group difference not assessed The RCT had large loss to follow-up (no further data reported)		
[68] RCT	51 people with moderate acne In review [17] [61]	**Reduction in inflammatory lesions , 6 months** 50% with doxycycline 20 mg twice daily 30% with placebo	P = 0.04	○○○	Doxycycline
Non-inflammatory lesions					
[68] RCT	51 people with moderate acne	**Reduction in comedones , 6 months**	P <0.01	○○○	Doxycycline

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	In review [17] [61]	54% with doxycycline 20 mg twice daily 11% with placebo			

Patient perception of improvement

Oral doxycycline compared with placebo We don't know whether oral doxycycline is more effective at improving patient perception of acne at 6 months in people with moderate acne (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient perception of improvement					
[68] RCT	51 people with moderate acne In review [17] [61]	**Patient perception of improvement , 6 months** 4.8 with doxycycline 20 mg twice daily 5.3 with placebo Global assessment scores measured on a scale from 1 to 7 where 1 = clear or almost clear skin	Reported as not significant P value and CI not reported	⟷	Not significant

No data from the following reference on this outcome. [67]

Psychological distress

No data from the following reference on this outcome. [67] [68]

Quality of life

No data from the following reference on this outcome. [67] [68]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[67] RCT **Crossover design**	62 people with mild acne In review [16] [61]	**Adverse effects** with oral doxycycline 100 mg daily with placebo The RCT found no adverse effects in people taking doxycycline or placebo	The RCT had large loss to follow-up (no further data reported) The RCT may have been underpowered to detect a difference in adverse effects		

No data from the following reference on this outcome. [68]

Oral doxycycline versus oral erythromycin:
See option on oral erythromycin, p 43 .

Oral doxycycline versus oral minocycline:
See option on oral minocycline, p 47 .

Oral doxycycline versus oral oxytetracycline:
We found one double-blind RCT. [69]

Acne severity

Oral doxycycline compared with oral oxytetracycline We don't know how oral doxycycline and oral oxytetracycline compare at reducing the number of lesions at 8 weeks in people with moderate to severe acne (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall severity					
[69] RCT **Crossover design**	28 people with moderate to severe acne	**Mean number of lesions per person , 8 weeks** 62 with oral doxycycline (100 mg daily for 8 weeks) 32 with oral oxytetracycline (250 mg 3 times daily for 4 weeks then once daily for 4 weeks) Pre-crossover results	Reported as not significant P value not reported	⟷	Not significant

Patient perception of improvement

No data from the following reference on this outcome. [69]

Psychological distress

No data from the following reference on this outcome. [69]

Quality of life

No data from the following reference on this outcome. [69]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[69] RCT **Crossover design**	28 people with moderate to severe acne	**Adverse effects** with oral doxycycline (100 mg daily for 8 weeks) with oral oxytetracycline (250 mg 3 times daily for 4 weeks then once daily for 4 weeks) The RCT reported no "significant adverse effects"			

Further information on studies

Comment: See comment on oral erythromycin regarding antibiotic resistance, p 38 .

Clinical guide:
Oral antibiotics are indicated as treatment for moderate acne that does not respond to topical treatments, and can be supplemented by non-antibiotic topical treatment (e.g., benzoyl peroxide) if needed. Oral tetracyclines (doxycycline, lymecycline, minocycline, oxytetracycline, tetracycline) offer benefits, but have differing adverse-effect profiles that need to be considered in treatment decisions. Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. [70] [71] Oral antibiotics may cause failure of oral contraceptives during the initial weeks of treatment.

OPTION LYMECYCLINE (ORAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Oral lymecycline is considered useful for people with more severe acne, although we don't know for sure whether it is effective.
- Oral antibiotics can cause adverse effects such as contraceptive failure.
- Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. They may cause contraceptive failure during the initial weeks of treatment.

Benefits and harms

Oral lymecycline versus placebo:

We found one systematic review (search date 1999), which identified no RCTs comparing oral lymecycline versus placebo. [16] We found no subsequent RCTs.

Oral lymecycline versus oral minocycline:

See option on oral minocycline, p 47 .

Further information on studies

Comment: **Clinical guide:**
Oral antibiotics are indicated as treatment for moderate acne that does not respond to topical treatments, and may be supplemented by non-antibiotic topical treatment (e.g., benzoyl peroxide) if needed. Oral tetracyclines (doxycycline, lymecycline, minocycline, oxytetracycline, tetracycline) are beneficial, but have different adverse-effect profiles that need to be considered in treatment decisions. Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. [70] [71] Oral antibiotics may cause failure of oral contraceptives during the initial weeks of treatment.

OPTION MINOCYCLINE (ORAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Oral minocycline is considered useful for people with more severe acne, although we don't know for sure whether it is effective.
- Oral antibiotics can cause adverse effects such as contraceptive failure.
- Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women.
- Minocycline has been associated with an increased risk of systemic lupus erythematosus, and of liver disorders.

Benefits and harms

Oral minocycline versus placebo:

We found one systematic review (search date 2002), [73] which identified one crossover RCT. We also found a pooled analysis of 3 RCTs comparing minocycline (extended-release formulation) versus placebo, reported in one publication. [74] One of the RCTs was a 4-armed phase 2 trial comparing minocycline at 3 different doses (1, 2, or 3 mg/kg/day) versus placebo; however, only the data on minocycline 1 mg/kg/day versus placebo (114 people) were included in the pooled analysis. The other two RCTs (924 people) were phase 3 trials comparing minocycline 1 mg/kg/day versus placebo. For additional information on harms of minocycline, in particular systemic lupus erythematosus and liver toxicity from observational studies, see comments.

Acne severity

Oral minocycline compared with placebo Oral minocycline may be more effective at reducing the number of inflammatory lesions and total number of lesions at 12 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall severity					
[75] RCT **Crossover design**	50 people, 43 completed In review [73]	**Total lesion score (compared with baseline score of 100%) , 5 weeks** 60% with oral minocycline (200 mg daily for first 7 days, then 100 mg daily) 84% with placebo Absolute results not reported Before crossover, it found that minocycline significantly reduced total lesion score from baseline (P <0.05), whereas placebo did not (no further data reported)	No direct comparison between groups The RCT was of insufficient duration to adequately assess the effects of minocycline		
[74] Pooled analysis of 3 RCTs	1038 people with moderate or severe facial acne	**Reduction from baseline in total number of lesions , 12 weeks** 33% with extended-release minocycline (1 mg/kg daily) 22% with placebo Absolute numbers not reported	P <0.001	○○○	Minocycline

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Inflammatory lesions					
[74] Pooled analysis of 3 RCTs	1038 people with moderate or severe facial acne	**Reduction in number of inflammatory lesions from baseline , 12 weeks** 46% with extended-release minocycline (1 mg/kg daily) 32% with placebo Absolute numbers not reported	P <0.001	○○○	Minocycline

Patient perception of improvement

No data from the following reference on this outcome. [75] [74]

Psychological distress

No data from the following reference on this outcome. [75] [74]

Quality of life

No data from the following reference on this outcome. [75] [74]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall adverse effects					
[74] Pooled analysis of 3 RCTs	1038 people with moderate or severe facial acne	**Adverse effects , 12 weeks** 56% with minocycline 54% with placebo The most commonly reported adverse effects in the minocycline group were headaches (22.6%), nausea (9.5%), fatigue (9.2%), dizziness (8.8%), diarrhoea (5.2%), and pruritus (4.6%)	Significance not assessed		

No data from the following reference on this outcome. [75]

Oral minocycline versus oral doxycycline:

We found two systematic reviews (search dates 2002, 5 RCTs; [73] 2006, 1 RCT [also identified by the first review] [72]) comparing oral minocycline versus oral doxycycline. The first review did not perform a meta-analysis because of heterogeneity among the trials in methods, outcomes assessed, and drug doses. It found problems with the methods used in all of the RCTs: 3 were open label, and the two double-blind RCTs reported insufficient information

to allow calculation of effect sizes. [73] Similarly, the second systematic review did not perform a meta-analysis. [72] Only one RCT (identified by both reviews) fulfilled *Clinical Evidence* inclusion criteria. [76]

Acne severity

Oral minocycline compared with oral doxycycline We don't know how oral minocycline and oral doxycycline compare at decreasing the total number of lesions or the number of papules or pustules, or open or closed comedones on the face, back, and chest after 12 weeks (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall severity					
[76] RCT Double-blind	79 people with mild to moderate inflammatory acne randomised, 64 people completed In review [73] [72]	**Number of all lesions on the face, back, and chest , 12 weeks** with oral minocycline with oral doxycycline Absolute results reported graphically Minocycline or doxycycline given as 50 mg twice daily for 4 weeks, then 50 mg once daily for 8 weeks (mean dosage 66 mg)	Reported as no significant difference	⟷	Not significant
Inflammatory lesions					
[76] RCT	79 people with mild to moderate inflammatory acne randomised, 64 people completed In review [73] [72]	**Number of papules and pustules on the face, back, and chest , 12 weeks** with oral minocycline with oral doxycycline Absolute results reported graphically Minocycline or doxycycline given as 50 mg twice daily for 4 weeks, then 50 mg once daily for 8 weeks (mean dosage 66 mg)	Reported as no significant difference	⟷	Not significant
Non-inflammatory lesions					
[76] RCT	79 people with mild to moderate inflammatory acne randomised, 64 people completed In review [73] [72]	**Number of all open comedones and closed comedones on the face, back, and chest , 12 weeks** with oral minocycline with oral doxycycline (mean dosage 66 mg) Absolute results reported graphically Minocycline or doxycycline given as 50 mg twice daily for 4 weeks, then 50 mg once daily for 8 weeks (mean dosage 66 mg)	Reported as no significant difference	⟷	Not significant

Patient perception of improvement

Oral minocycline compared with oral doxycycline We don't know how oral minocycline and oral doxycycline compare at increasing patient perception of improvement (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient perception of improvement					
[76] RCT	79 people with mild to moderate inflammatory acne randomised, 64 people completed In review [73] [72]	**Proportion of patients who evaluated treatment as effective or very effective , 12 weeks** 90% with oral minocycline 85% with oral tetracycline Absolute results reported graphically Minocycline or doxycycline given as 50 mg twice daily for 4 weeks, then 50 mg once daily for 8 weeks, (mean dosage 66 mg)	Statistical assessment not reported		

Psychological distress

No data from the following reference on this outcome. [76]

Quality of life

No data from the following reference on this outcome. [76]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[76] RCT	79 people with mild to moderate inflammatory acne randomised, 64 people completed In review [73] [72]	**Adverse effects , 12 weeks** with oral minocycline with oral doxycycline Absolute results reported graphically Both drugs described as generally well tolerated. Adverse effects causing discontinuation were dyspepsia (1 in each group), headache (1 with doxycycline), nausea (1 with minocycline), vertigo (1 with minocycline)			

Oral minocycline versus oral lymecycline:

We found two systematic reviews (search dates 2002, 2 RCTs [1 RCT also identified by the second review]; [73] 2006, 3 RCTs [72]) comparing oral minocycline versus oral lymecycline. Neither of the reviews pooled the data, and so we have reported those RCTs that agreed with *Clinical Evidence* inclusion criteria.

Acne severity

Oral minocycline compared with oral lymecycline Oral minocycline and oral lymecycline seem equally effective at 12 weeks at increasing the proportion of people with 50% or greater reduction in inflammatory or non-inflammatory lesions (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Total count					
[77] RCT	144 people with at least 20 inflammatory lesions on the face In review [73] [72]	**Overall reduction in total lesion count , 12 weeks** 43% with minocycline 45% with lymecycline	Reported as no significant difference between groups Intention-to-treat analysis	⟷	Not significant
[78] RCT	136 people randomised In review [72]	**Mean reduction in total lesion count from baseline , 12 weeks** –55% with minocycline (100 mg daily) –56% with lymecycline (300 mg daily) Absolute numbers not reported	Difference –0.29 95% CI –10.53 to +9.95 Intention-to-treat analysis	⟷	Not significant
Non-inflammatory lesions					
[77] RCT	144 people with at least 20 inflammatory lesions on the face In review [73] [72]	**Overall reduction in non-inflammatory lesion count , 12 weeks** 32% with minocycline 41% with lymecycline	P = 0.093 Intention-to-treat analysis	⟷	Not significant
[78] RCT	136 people randomised In review [72]	**Mean reduction in non-inflammatory lesion count from baseline , 12 weeks** –47% with minocycline (100 mg daily) – 54% with lymecycline (300 mg daily) Absolute numbers not reported	95% CI –23.8 to +8.1 Intention-to-treat analysis	⟷	Not significant
[79] RCT **3-armed trial**	86 people, 68 completed In review [72] The remaining arm evaluated minocycline (50 mg daily for 12 weeks)	**Total lesion count , 12 weeks** with minocycline (100 mg daily for 4 weeks followed by 50 mg daily for 8 weeks) with lymecycline (300 mg daily for 12 weeks) Absolute results reported graphically	P (minocycline 100 mg/50 mg *v* lymecycline) <0.05	○○○	Minocycline 100 mg/50 mg
[79] RCT **3-armed trial**	86 people, 68 completed (week 12) In review [72] The remaining arm evaluated minocycline (100 mg daily for 4 weeks followed by 50 mg daily for 8 weeks)	**Total lesion count , 12 weeks** with minocycline (50 mg daily for 12 weeks) with lymecycline (300 mg daily for 12 weeks) Absolute results reported graphically	Reported as no clinically relevant difference between minocycline 50 mg *v* lymecycline		
Inflammatory lesions					
[77] RCT	144 people with at least 20 inflammatory lesions on the face In review [73] [72]	**Overall reduction in inflammatory lesion count , 12 weeks** 52.2% with minocycline 50.6% with lymecycline	Reported as no significant difference between groups Intention-to-treat analysis	⟷	Not significant
[78] RCT	136 people randomised In review [72]	**Mean reduction in inflammatory count from baseline , 12 weeks**	Difference +2.32 95% CI –9.59 to +14.22 Intention-to-treat analysis	⟷	Not significant

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		–64.5% with minocycline (100 mg daily) –58.7% with lymecycline (300 mg daily) Absolute numbers not reported			

Patient perception of improvement

Oral minocycline compared with oral lymecycline Oral minocycline and oral lymecycline seem equally effective at 12 weeks at increasing the proportion of people who perceive an overall improvement in their acne (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient perception of improvement					
[77] RCT	144 people with at least 20 inflammatory lesions on the face In review [73] [72]	**Proportion of patients who considered their condition to have improved, much improved, or cleared , 12 weeks** 83% with minocycline 85% with lymecycline Absolute numbers not reported	Reported no significant difference between groups	⟷	Not significant
[78] RCT	136 people randomised In review [72]	**Proportion of patients who considered their condition to have improved, much improved, or cleared , 12 weeks** 44/68 (65%) with minocycline (100 mg daily) 57/66 (86%) with lymecycline (300 mg daily)			

Psychological distress

No data from the following reference on this outcome. [73]

Quality of life

No data from the following reference on this outcome. [73]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[78] RCT	136 people randomised In review [72]	**Proportion of people with at least 1 adverse effect , 12 weeks** 20/68 (29%) with minocycline (100 mg daily)			

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
		18/66 (27%) with lymecycline (300 mg daily) Adverse effects that were considered treatment-related included: headache, nausea, convulsion, dermatitis, diarrhoea, dyspepsia, myalgia, and pharyngitis with lymecycline; oral moniliasis, dermatitis, nausea, urticaria, and vaginitis with minocycline			

Oral minocycline versus oral oxytetracycline:

We found one systematic review (search date 2002), which identified one open-label RCT comparing oral minocycline versus oral oxytetracycline that did not meet *Clinical Evidence* inclusion criteria. [73] We found one subsequent RCT. [80]

Acne severity

No data from the following reference on this outcome. [80]

Patient perception of improvement

Oral minocycline compared with oral oxytetracycline Oral minocycline seems no more effective at increasing the proportion of people who report moderate improvement at 18 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient perception of improvement					
[80] RCT **5-armed trial**	649 people with mild to moderate acne (Leeds acne grade 3 or less) The remaining arms evaluated oral placebo plus topical benzoyl peroxide twice daily; oral placebo plus topical benzoyl peroxide plus topical erythromycin twice daily; and oral placebo plus topical erythromycin in the morning plus topical benzoyl peroxide in the evening	**Proportion of people reporting at least moderate improvement in facial acne , 18 weeks** 70/130 (54%) with oral minocycline 100 mg once daily plus topical placebo 72/131 (55%) with oral oxytetracycline 500 mg twice daily plus topical placebo Improvement assessed using a 6-point Likert scale	OR 0.95 95% CI 0.58 to 1.55	⟷	Not significant

Psychological distress

No data from the following reference on this outcome. [80]

Quality of life

No data from the following reference on this outcome. [80]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Skin adverse effects					
[80] RCT **5-armed trial**	649 people with mild to moderate acne (Leeds acne grade 3 or less) The remaining arms evaluated oral placebo plus topical benzoyl peroxide twice daily; oral placebo plus topical benzoyl peroxide plus topical erythromycin twice daily; and oral placebo plus topical erythromycin in the morning plus topical benzoyl peroxide in the evening	**Skin adverse effects , 18 weeks** 4% with oral minocycline 100 mg once daily plus topical placebo 4% with oral oxytetracycline 500 mg twice daily plus topical placebo Absolute numbers not reported	Significance not assessed		
Gastrointestinal adverse effects					
[80] RCT **5-armed trial**	649 people with mild to moderate acne (Leeds acne grade 3 or less) The remaining arms evaluated oral placebo plus topical benzoyl peroxide twice daily; oral placebo plus topical benzoyl peroxide plus topical erythromycin twice daily; and oral placebo plus topical erythromycin in the morning plus topical benzoyl peroxide in the evening	**Gastrointestinal adverse effects , 18 weeks** 9% with oral minocycline 100 mg once daily plus topical placebo 8% with oral oxytetracycline 500 mg twice daily plus topical placebo Absolute numbers not reported	Significance not assessed		
Central nervous system adverse events					
[80] RCT **5-armed trial**	649 people with mild to moderate acne (Leeds acne grade 3 or less) The remaining arms evaluated oral placebo plus topical benzoyl peroxide twice daily; oral placebo plus topical ben-	**Central nervous system adverse events , 18 weeks** 11% with oral minocycline 100 mg once daily plus topical placebo 17% with oral oxytetracycline 500 mg twice daily plus topical placebo Absolute numbers not reported	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
	zoyl peroxide plus topical erythromycin twice daily; and oral placebo plus topical erythromycin in the morning plus topical benzoyl peroxide in the evening				
Musculoskeletal symptoms					
[80] RCT **5-armed trial**	649 people with mild to moderate acne (Leeds acne grade 3 or less) The remaining arms evaluated oral placebo plus topical benzoyl peroxide twice daily; oral placebo plus topical benzoyl peroxide plus topical erythromycin twice daily; and oral placebo plus topical erythromycin in the morning plus topical benzoyl peroxide in the evening	**Proportion of people with musculoskeletal symptoms , week 12** 2% with oral minocycline 100 mg once daily plus topical placebo with oral oxytetracycline 500 mg twice daily plus topical placebo Absolute numbers not reported Figures not reported for other groups			
[80] RCT **5-armed trial**	649 people with mild to moderate acne (Leeds acne grade 3 or less) The remaining arms evaluated oral placebo plus topical benzoyl peroxide twice daily; oral placebo plus topical benzoyl peroxide plus topical erythromycin twice daily; and oral placebo plus topical erythromycin in the morning plus topical benzoyl peroxide in the evening	**Proportion of people with musculoskeletal symptoms , week 18** 4% with oral minocycline 100 mg once daily plus topical placebo with oral oxytetracycline 500 mg twice daily plus topical placebo Absolute numbers not reported Figures not reported for other groups			

Oral minocycline versus oral tetracycline:

We found two systematic reviews (search dates 2002, 6 RCTs; [73] 2006, 5 RCTs [all of which were also identified by the first review] [72]) comparing oral minocycline versus oral tetracycline. The reviews did not perform meta-analyses because of heterogeneity among the trials in outcomes assessed. We have reported those RCTs that satisfy *Clinical Evidence* inclusion criteria.

Acne severity

Oral minocycline compared with oral tetracycline Oral minocycline and oral tetracycline seem equally effective at improving overall acne severity assessed on a variety of scales (including the Samuelson Lesion Scale) (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall severity					
[73] Systematic review Double-blind	100 people randomised, 82 people completed Data from 1 RCT	**Investigator assessed improvement , 12 weeks** 32/50 (64%) with minocycline (100 mg daily) 36/50 (72%) with tetracycline (500 mg daily)	OR 0.69 95% CI 0.30 to 1.61 (Absolute numbers and statistics from systematic review as we were unable to access the original text of this RCT)	⟷	Not significant
[81] RCT Double-blind	62 college students with moderate to severe inflammatory acne In review [73] [72]	**Investigator assessed severity scores (change from baseline) , 12 weeks** from 5.50 to 2.88 with minocycline (50 mg twice daily) from 5.04 to 2.85 with tetracycline (250 mg twice daily) Severity of acne was graded according to the Samuelson nine-grade global acne scale: 9 photographs of patients with acne attributed score from 1 (sparse comedones with little or no inflammatory process noticeable) to 9 (deep cysts, inflammatory nodules, or both present)	Reported as no significant difference between groups	⟷	Not significant

Patient perception of improvement

Oral minocycline compared with oral tetracycline We don't know how oral minocycline and oral tetracycline compare at increasing the proportion of people with moderate to severe acne who report an overall improvement or rate response as satisfactory (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient perception of improvement					
[81] RCT Double-blind	62 college students with moderate to severe inflammatory acne In review [73] [72]	**Patient assessed severity scores (change from baseline) , 12 weeks** from 5.32 to 3.27 with minocycline (50 mg twice daily) from 4.89 to 3.48 with tetracycline (250 mg twice daily) Severity of acne was graded according to the Samuelson nine-grade global acne scale: 9 photographs of patients with acne attributed score from 1 (sparse comedones with little or no inflammatory process noticeable) to 9 (deep cysts, inflammatory nodules, or both present)	Reported as no significant difference between groups	⟷	Not significant
[73] Systematic review Double-blind	100 people randomised, 82 people completed Data from 1 RCT	**Patient perception of improvement , 20 weeks** with minocycline (100 mg daily) with tetracycline (500 mg daily)		⟷	Not significant

Psychological distress

No data from the following reference on this outcome. [73]

Quality of life

No data from the following reference on this outcome. [73]

Adverse effects

No data from the following reference on this outcome. [73]

Further information on studies

Comment: See comment on oral erythromycin regarding antibiotic resistance, p 38 .

Adverse effects: We found 3 systematic reviews assessing the adverse effects of minocycline. [73] [82] [83] The first review (search date 2002) pooled data on adverse effects of minocycline from 21 RCTs examining minocycline versus control (placebo or other oral or topical treatments). [73] It found that 137/1230 (11%) people had an adverse reaction attributed to minocycline, 36/1230 (3%) of whom withdrew because of adverse effects. It also found that 17/700 (2%) people taking minocycline had abnormal pigmentation. [73] One prospective cohort study identified by the review (700 people) assessed adverse effects in people taking minocycline 100 to 200 mg daily for a mean 10.5 months. [84] It found that adverse effects were reported in 13.6% of people. They included vestibular disturbance, candida infection, gastrointestinal disturbance, cutaneous symptoms (pigmentation, pruritus, photosensitive rash, and urticaria), and benign intracranial hypertension.
Systemic lupus erythematosus (SLE): We found two systematic reviews. [73] [82] The first review [73] identified one case control study [85] (27,688 people aged 15–19 years with acne) assessing the risk of SLE in people taking tetracyclines compared with matched controls. Women had a significantly higher risk of developing SLE compared with men (RR 14, 95% CI 1.8 to 111). The case control study found that 29 people (27 women) taking tetracyclines had an SLE-like syndrome. It found that current minocycline use significantly increased the risk of developing SLE (AR 52.8 cases per 100,000 prescriptions; RR 8.5, 95% CI 2.1 to 35). It found no significant difference in the risk of developing SLE with tetracyclines other than minocycline, although use of tetracyclines was associated with an increased risk (RR 1.7, 95% CI 0.4 to 8.1). Cumulative minocycline dose and prolonged exposure (more than 100 days) to minocycline may also be risk factors, but no quantitative data were reported. The second review (search date 1999) identified 57 case reports of SLE in people taking minocycline. [82] It suggested that minocycline may induce SLE, but did not quantify its conclusions. Evidence about adverse effects should be interpreted with caution because of wide variation between studies in numbers of reported adverse events. The prevalence of SLE in the general population is 30/100,000 in white people, rising to 200/100,000 in Afro-Caribbean people. [86]
Liver damage: We found one systematic review (search date 1998) of case reports and case series, which found 65 cases of liver damage in people taking minocycline. [83] The review did not quantify the increased risk in people taking minocycline. It suggested that minocycline was associated with severe hepatic dysfunction, including hypersensitivity, within a few weeks of taking minocycline (16 cases), autoimmune hepatitis within 1 year or more of taking minocycline (29 cases), or unspecified hepatitis (20 cases).
Clinical guide:
Oral antibiotics are indicated as treatment for moderate acne that does not respond to topical treatments, and may be supplemented by non-antibiotic topical treatment (e.g., benzoyl peroxide) if needed. Oral tetracyclines (doxycycline, lymecycline, minocycline, oxytetracycline, tetracycline) are beneficial, but have different adverse-effect profiles that need to be considered in treatment decisions. Current clinical guidance in the UK suggests that people taking minocycline for more than 6 months should be monitored for hepatotoxicity, pigmentation, and SLE. [87] Tetracyclines

may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. [70] [71] They may cause contraceptive failure during the initial weeks of treatment.

OPTION OXYTETRACYCLINE (ORAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Oral oxytetracycline is considered useful for people with more severe acne, although we don't know for sure whether it is effective.
- Oral antibiotics can cause adverse effects such as contraceptive failure.
- Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women.

Benefits and harms

Oral oxytetracycline versus placebo:

We found one systematic review (search date not reported), [61] which identified no RCTs comparing oral oxytetracycline versus placebo. We found no subsequent RCTs.

Oral oxytetracycline versus oral minocycline:

See option on oral minocycline, p 47 .

Oral oxytetracycline versus oral doxycycline:

See option on oral doxycycline, p 43 .

Further information on studies

Comment: See comment on oral erythromycin regarding antibiotic resistance, p 38 .

Clinical guide:
Oral antibiotics are indicated as treatment for moderate acne that does not respond to topical treatments, and may be supplemented by non-antibiotic topical treatment (e.g., benzoyl peroxide) if needed. Oral tetracyclines (doxycycline, lymecycline, minocycline, oxytetracycline, tetracycline) are beneficial, but have different adverse-effect profiles that need to be considered in treatment decisions. Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. [70] [71] Oral antibiotics may cause failure of oral contraceptives during the initial weeks of treatment.

OPTION TETRACYCLINE (ORAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Oral tetracycline is considered useful for people with more severe acne, although we don't know for sure whether it is effective. Oral antibiotics can cause adverse effects such as contraceptive failure.
- Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women.

Benefits and harms

Oral tetracycline versus placebo:

We found 3 systematic reviews. [16] [17] [61] The first review (search date 1999, 7 RCTs, 864 people with mild, moderate, or severe acne) compared oral tetracycline 250 mg twice daily versus placebo. [16] The review did not perform a meta-analysis because of heterogeneity among the trials in outcomes assessed. The second review

(search date 2004), [17] which had more stringent inclusion criteria, identified one RCT included in the earlier review. [23] The third review (search date not reported) did not include any further RCTs. [61]

Acne severity

Oral tetracycline compared with placebo Oral tetracycline may be more effective at reducing severity of acne at 6 to 13 weeks in people with acne (very low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Overall severity					
[26] RCT **3-armed trial**	367 people with moderate to severe acne In review [16] The remaining arm evaluated clindamycin phosphate 1%	**Proportion for whom physician assessment of treatment was "excellent" or "good"** 64% with oral tetracycline 46% with placebo Unclear how assessment by physician was defined Completer analysis of 305/367 (83%) people who completed the trial	P <0.05	○○○	Tetracycline
[57] RCT **3-armed trial** Only observer blinded	75 people with moderate acne In review [16] The remaining arm evaluated topical tetracycline 0.5% plus oral placebo	**Mean reduction in acne severity grade measured on a scale from 0 (least severe) to 8 (most severe) , 6 weeks** 1.14 with oral tetracycline 250 mg twice daily plus topical placebo 0.43 with topical plus oral placebo 11/75 (15%) people withdrew from the trial; no intention-to-treat analysis	P <0.05	○○○	Tetracycline
[57] RCT **3-armed trial** Only observer blinded	75 people with moderate acne In review [16] The remaining arm evaluated topical tetracycline 0.5% plus oral placebo	**Mean reduction in acne severity grade measured on a scale from 0 (least severe) to 8 (most severe) , 13 weeks** 1.91 with oral tetracycline 250 mg twice daily plus topical placebo 0.62 with topical plus oral placebo 11/75 (15%) people withdrew from the trial; no intention-to-treat analysis	P <0.05	○○○	Tetracycline
[58] RCT **3-armed trial**	60 male adolescents with mild to moderate acne In review [16] The remaining arm evaluated oral placebo plus topical tetracycline	**Improvement from baseline of 1 or more on a scale from 0 to 8 , 8 weeks** 12/18 (67%) with oral tetracycline plus topical vehicle 6/17 (35%) with oral placebo plus topical vehicle	Significance not assessed		
[59] RCT **3-armed trial**	135 people aged 18 to 25 years with mild to moderate acne, Cook's grades 0 to 8 In review [16] The remaining arm evaluated topical tetracycline 0.22% plus oral placebo	**Acne severity , 7 weeks** with oral tetracycline plus topical vehicle with topical vehicle plus oral placebo Absolute results reported graphically	P <0.05	○○○	Tetracycline

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[59] RCT **3-armed trial**	135 people aged 18 to 25 years with mild to moderate acne, Cook's grades 0 to 8 In review [16] The remaining arm evaluated topical tetracycline 0.22% plus oral placebo	**Acne severity , 10 weeks** with oral tetracycline plus topical vehicle with topical vehicle plus oral placebo Absolute results reported graphically	P <0.05	○○○	Tetracycline
[59] RCT **3-armed trial**	135 people aged 18 to 25 years with mild to moderate acne, Cook's grades 0 to 8 In review [16] The remaining arm evaluated topical tetracycline 0.22% plus oral placebo	**Acne severity , 12 weeks** with oral tetracycline plus topical vehicle with topical vehicle plus oral placebo Absolute results reported graphically	P <0.05	○○○	Tetracycline
[88] RCT	51 people (severity of acne unclear) In review [16]	**Change in Pillsbury modified score , 12 weeks** –2 with tetracycline 250 mg twice daily 0 with placebo Pillsbury modified score: assigns 1 point for a change equivalent to half a grade. Score of +1 to +4 = "improved", 0 = "no change", and –1 to –4 = "worse" See further information on studies for details on patient improvement	P = 0.001	○○○	Tetracycline
[88] RCT	51 people (severity of acne unclear) In review [16]	**Proportion of people assessed as "improved" , 12 weeks** 23/24 (96%) with tetracycline 250 mg twice daily 15/27 (56%) with placebo See further information on studies for details on patient improvement	P = 0.01	○○○	Tetracycline
Inflammatory lesions					
[23] RCT **3-armed trial**	108 people with mild to moderate acne In review [16] [17] The remaining arm evaluated clindamycin phosphate 1% twice daily	**Mean inflammatory lesion count (change from baseline) , 8 weeks** 2.66 with oral tetracycline 500 mg twice daily 6.24 with placebo Completer analysis in 87 people, no intention-to-treat analysis performed Oral tetracycline significantly reduced inflammatory lesion count from baseline (P = 0.0001), but placebo did not	Significance of between-group difference not assessed RCT designed to compare oral tetracycline *v* topical clindamycin		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[89] RCT **4-armed trial**	68 people with mild to moderate acne In review [16] The remaining arms evaluated ibuprofen plus placebo and tetracycline plus ibuprofen	**Percentage reduction in inflammatory lesions , 8 weeks** 26% with tetracycline plus placebo 16% with placebo	Reported as not significant P value not reported RCT may have lacked power to detect a clinically important difference among groups	⟷	Not significant

Patient perception of improvement

Oral tetracycline compared with placebo Oral tetracycline seems more effective at increasing the proportion of people with moderate to severe acne who perceive their acne as markedly improved or improved at 8 weeks (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Patient perception of improvement					
[23] RCT **3-armed trial**	108 people with mild to moderate acne In review [16] [17] The remaining arm evaluated clindamycin phosphate 1% twice daily	**"Markedly improved" or "improved" from baseline** 72% with oral tetracycline 500 mg twice daily 3% with placebo Completer analysis in 87 people; no intention-to-treat analysis performed	Significance of between-group difference not assessed RCT designed to compare oral tetracycline *v* topical clindamycin		
[26] RCT **3-armed trial**	367 people with moderate to severe acne In review [16] The remaining arm evaluated clindamycin phosphate 1%	**Proportion of people who thought their acne was "markedly improved" or "improved"** 84% with oral tetracycline 57% with placebo Unclear how assessment by patient was defined Completer analysis in 305/367 (83%) people who completed the trial	P <0.05	○○○	Tetracycline

No data from the following reference on this outcome. [57] [58] [59] [88] [89]

Psychological distress

No data from the following reference on this outcome. [23] [26] [57] [58] [59] [88] [89]

Quality of life

No data from the following reference on this outcome. [23] [26] [57] [58] [59] [88] [89]

Adverse effects

No data from the following reference on this outcome. [23] [26] [57] [58] [59] [88] [89]

Oral tetracycline versus oral erythromycin:
See option on oral erythromycin, p 38 .

Oral tetracycline versus oral minocycline:
See option on oral minocycline, p 47 .

Oral tetracycline versus oral isotretinoin:
See option on oral retinoids, p 62

Further information on studies

[88] The RCT reported in the discussion section of the article that patient perception of improvement was "close" to clinical assessment; no further data provided.

Comment: See comment on oral erythromycin regarding antibiotic resistance, p 38 .

Clinical guide:
Oral antibiotics are indicated as treatment for moderate acne that does not respond to topical treatments, and may be supplemented by non-antibiotic topical treatment (e.g., benzoyl peroxide) if needed. Oral tetracyclines (doxycycline, lymecycline, minocycline, oxytetracycline, tetracycline) are beneficial, but have different adverse-effect profiles that need to be considered in treatment decisions. Tetracyclines may harm bones and teeth, and should not be taken by pregnant or breastfeeding women. Oral antibiotics may cause failure of oral contraceptives during the initial weeks of treatment.

OPTION ISOTRETINOIN (ORAL)

- For GRADE evaluation of interventions for Acne vulgaris, see table, p 69 .
- Oral isotretinoin is teratogenic and is associated with a wide range of adverse effects, such as skin problems, changes in liver function, and development of psychiatric disorders.

Benefits and harms

Oral isotretinoin versus placebo:
We found one RCT. [90] For additional information from observational studies on harms of isotretinoin, see comment.

Acne severity

Oral isotretinoin compared with placebo Oral isotretinoin is more effective at reducing nodules at 1 month in people with treatment-resistant cystic and conglobate acne (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Nodules					
[90] RCT	33 people with treatment-resistant cystic and conglobate acne	**Mean change in nodules , 1 month** –32% with oral isotretinoin (0.5 mg/kg/day) +33% with placebo group Absolute numbers not reported RCT had extended open phase; see further information on studies for full details	P <0.008	○○○	Isotretinoin

Patient perception of improvement

No data from the following reference on this outcome. [90]

Psychological distress

No data from the following reference on this outcome. [90]

Quality of life

No data from the following reference on this outcome. [90]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[90] RCT	33 people with treatment-resistant cystic and conglobate acne	**Adverse effects** with oral isotretinoin (0.5 mg/kg/day) with placebo group Absolute results not reported The RCT found low rates of adverse effects in the isotretinoin group, including arthralgia, decreased appetite, fatigue, cheilitis, facial dermatitis, conjunctivitis, xerosis, and dryness of the nasal mucosa with nosebleeds. No one stopped treatment owing to adverse effects			

Oral isotretinoin versus oral tetracycline:

We found one small RCT. [91] For additional information from observational studies on harms of isotretinoin, see comment.

Acne severity

Oral isotretinoin compared with oral tetracycline Oral isotretinoin is more effective at reducing acne cysts, pustules, and comedones at 24 weeks in people with severe nodulocystic acne (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Inflammatory lesions					
[91] RCT	29 people with severe nodulocystic acne	**Reduction in acne cysts , 24 weeks** 82% with oral isotretinoin (1–2 mg/kg/day) 52% with oral tetracycline (0.5–1 mg/day) Absolute numbers not reported	P <0.01	○○○	Isotretinoin
[91] RCT	29 people with severe nodulocystic acne	**Reduction in pustules and comedones , 24 weeks** 85% with oral isotretinoin (1–2 mg/kg/day) 58% with oral tetracycline (0.5–1 mg/day) Absolute numbers not reported	P <0.01	○○○	Isotretinoin

Patient perception of improvement

No data from the following reference on this outcome. [91]

Psychological distress

No data from the following reference on this outcome. [91]

Quality of life

No data from the following reference on this outcome. [91]

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Adverse effects					
[91] RCT	29 people with severe nodulocystic acne	**Xerosis** 15/15 (100%) with isotretinoin 2/15 (13%) with oral tetracycline	Significance not assessed		

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
[91] RCT	29 people with severe nodulocystic acne	**Cheilitis/dry lips** 15/15 (100%) with isotretinoin 3/15 (20%) with oral tetracycline	Significance not assessed		
[91] RCT	29 people with severe nodulocystic acne	**Dry nose** 10/15 (67%) with isotretinoin 1/15 (7%) with oral tetracycline	Significance not assessed		
[91] RCT	29 people with severe nodulocystic acne	**Dry mouth** 3/15 (20%) with isotretinoin 1/15 (7%) with oral tetracycline	Significance not assessed		
[91] RCT	29 people with severe nodulocystic acne	**Adverse effects (other)** with isotretinoin with oral tetracycline Absolute results not reported The RCT also reported desquamation, alopecia, erythema, pruritus, epistaxis, dry eyes, conjunctivitis, pterygium (right eye), and photophobia in the isotretinoin group	Significance not assessed		

Further information on studies

[90] An open phase extension to this RCT for a further 2 to 4 months showed further improvement in the treatment group as dose increased to a mean of 0.9 mg/kg/day.

Comment:

Skin: Dry skin and mucosal surfaces are a well-known adverse effect of isotretinoin treatment. We found one open study (80 people with a range of acne types failing to respond to oral antibiotics) of intermittent dosing with isotretinoin 0.5 mg/kg/daily (1 week in 4 for 6 months), to determine the relative efficacy versus adverse effects. [92] Although there was no control group, the authors reported modest cheilitis at the lower end of the spectrum for isotretinoin adverse effects. [92]

Liver function: Isotretinoin treatment affects the metabolic system, and is reflected in altered liver function tests and elevated blood lipids. We found one retrospective analysis of people receiving isotretinoin for acne to determine the necessity for routine testing of lipid profiles and liver function during treatment. The 209 people in the study included 113 people treated with 1 mg/kg/day, and 96 people treated with 0.5 mg/kg/day, who had serial fasting blood samples taken at 0, 8, and 16 weeks. The study found no significant changes in any of the tests of liver function. It concluded that, if the baseline tests are normal, in the absence of clinical indicators or doses greater than 1 mg/kg, it is safe to measure just once at about 4 weeks. For prolonged doses, or where there are pre-existing abnormalities or higher doses, more frequent testing may be warranted. [93]

Pregnancy (teratogenesis): Isotretinoin is teratogenic. We found two studies evaluating the effect of isotretinoin treatment on pregnancy and unborn infants. The first study (24,503 women self-registered for a pregnancy prevention programme) found that, in 402 pregnancies, 32 went to term; 13 of the infants were examined for teratogenic effects, revealing changes in 5/32. [94] In the second study (8609 women), 90 women became pregnant, with 9 women progressing to live birth. One of the 9 infants had a congenital anomaly of the neck and face. [95] It is not clear how many of the 76/90 terminated pregnancies had already identified anomalies by ultrasound that might have biased the results.

Psychiatric adverse effects: There is controversy and conflicting evidence on the association of isotretinoin with a variety of adverse psychiatric effects. We found two systematic reviews (search dates 2004; [96] not reported [97]). The first review included one prospective survey [98] and one case control study [99] that was also included in the second review, on psychiatric adverse effects

with isotretinoin. The prospective survey reported that the manufacturers had supplied 12 million treatments of isotretinoin by 2001. The data on adverse effects documented 1247 people with mood disorders. The authors also had records of 168 people with suicidal behaviour, 104 with suicide attempts, and 64 with completed suicides, at 10 years' follow-up after the completion of medication. Thirty suicides were confirmed in people while taking the medication. However, this figure should be considered in the context of a very large denominator. In addition, behavioural disorders and suicides are relatively common in the age group typically taking isotretinoin. US healthcare data reviewed in the same publication noted that 5 million people in the US are taking isotretinoin. The number of suicides expected in that group from national standardised rates would be 190, whereas the number actually reported was 37. [98] The second systematic review included 6 prospective studies (of which 2 were RCTs [158 people], 3 were cohort studies [272 people], and 1 was a descriptive study [189 people]) and 3 retrospective studies (of which 2 were cohort studies [32,092 people], and 1 was a descriptive study [877 people]). A total of 9 studies examined the association between isotretinoin and depression, whereas only two studies examined the association between isotretinoin and suicidal behaviour. The review concluded that overall no association could be demonstrated between risk of depression or suicidal behaviour and use of isotretinoin. However, it was acknowledged that all included studies fell short of providing a definitive answer, mainly through small size and difficulties in randomisation and blinding. The review authors commented that more than 100,000 people and long-term follow-up would be needed in an RCT to provide conclusive evidence about an association between isotretinoin and suicide. [97] We found one subsequent cohort study indicating a lack of association between isotretinoin and suicidal thoughts or action. In spite of this, there remain clinical concerns that isotretinoin might be associated with idiosyncratic adverse mood and behavioural effects in a small number of people. This means that guidelines for use and the drug licence include an outline psychiatric history and assessment undertaken by the dermatologist, with relevant monitoring questions at each consultation.

Clinical guide: Many of the studies reported here are from the 1990s, assessing data from the 1980s. At that time, the threshold for prescribing oral isotretinoin was higher, where it was typically used on more severe acne. The norms have since shifted, such that it may well be that the milder grades of acne may be effectively managed with lower doses. In addition, adverse effects (see harms, above) may warrant a trial of different regimens in order to achieve clearance with less discomfort. Clinical experience demonstrates that oral isotretinoin is an immensely valuable drug in the management of complex and aggressive acne. It shortens the duration of suffering, and typically reduces the amount of scarring. However, adverse effects are common and sometimes severe. People in their 20s or older may relapse more frequently than adolescents with similar treatment. Those with milder acne may need smaller doses, but the data on the degree of improvement are not as clear for this group as they are in classic severe nodulocystic acne. Measures to prevent pregnancy and screen for psychological factors were revised in 2005, with changes to the drug licence, effective in the US and EU. [100] The current "pregnancy protection programme" recommends monthly pregnancy tests from 1 month before treatment to 1 month after the end of treatment, the use of two different forms of contraception, and the issue of prescriptions for only 4 weeks' medication at a time. The oral contraceptive, or co-cyprindiol, may be commenced before treatment of women of child-bearing age with isotretinoin, and continued for at least 1 month after. This provides some additional and independent therapeutic effect in some instances. As documented in harms (see above), there remains uncertainty about the relevance of isotretinoin treatment to adverse psychological events and suicide. However, it remains important that the medical history and monitoring take close note of psychiatric history and symptoms when reviewed in clinic. One systematic review from primary care suggested that, although the general practitioner (GP) was best placed to undertake this, it would introduce potential for error through communication between the GP and dermatologist, where the dermatologist would be responsible for prescribing. [100]

GLOSSARY

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Adapalene (topical) New evidence added. [48] Categorisation unchanged (Likely to be beneficial).

Doxycycline (oral) New evidence added. [72] Categorisation unchanged (Trade-off between benefits and harms).

Lymecycline (oral) New evidence added. [72] Categorisation unchanged (Trade-off between benefits and harms).

Minocycline (oral) New evidence added. [72] Categorisation unchanged (Trade-off between benefits and harms).

Tetracycline (oral) New evidence added. [72] Categorisation unchanged (Trade-off between benefits and harms).

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Disclaimer

GRADE **Evaluation of interventions for Acne vulgaris.**

Important outcomes			Acne severity, Patient perception of improvement, Psychological distress, Quality of life						
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of topical treatments in people with acne vulgaris?									
5 (less than 875) [19] [18] [20] [21] [22]	Acne severity	Topical benzoyl peroxide versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for assessing different outcomes and for no direct comparison between groups in one RCT
7 (less than 1284) [18] [23] [25] [26] [27] [28]	Acne severity	Topical clindamycin versus placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and methodological flaws (no intention-to-treat analysis, or poor follow-up)
3 (less than 750) [23] [27] [26]	Patient perception of improvement	Topical clindamycin versus placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and methodological flaws (no intention-to-treat analysis, poor follow-up)
8 (less than 1108) [32] [33] [34] [35] [36] [37] [27] [39]	Acne severity	Topical erythromycin versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for assessing different outcomes
1 (less than 160) [32]	Patient perception of improvement	Topical erythromycin versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no direct comparison between groups
4 (less than 999) [40] [41] [43] [44]	Acne severity	Topical tretinoin versus placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and no intention-to-treat analysis
1 (60) [42]	Patient perception of improvement	Topical tretinoin versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no direct comparison between groups
4 (1343) [49] [46] [47] [48]	Acne severity	Topical adapalene versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (453) [46] [48]	Patient perception of improvement	Topical adapalene versus placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and no statistical comparison between groups in one RCT.
2 (132) [50] [51]	Acne severity	Azelaic acid versus placebo	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for uncertainty about duration and severity of acne in one RCT
2 (less than 222) [53] [54]	Acne severity	Topical erythromycin plus zinc versus placebo	4	0	0	–2	0	Low	Directness points deducted for uncertainty about severity of acne in one RCT and for assessing different outcomes
4 (less than 632) [20] [55] [56] [32]	Acne severity	Topical isotretinoin versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct comparison between groups

Important outcomes	Acne severity, Patient perception of improvement, Psychological distress, Quality of life								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (less than 160) [32]	Patient perception of improvement	Topical isotretinoin versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no direct comparison between groups
4 (less than 344) [57] [58] [59] [60]	Acne severity	Topical tetracycline versus placebo	4	–3	0	0	0	Very low	Quality points deducted for incomplete reporting of results and for methodological flaws (no intention-to-treat analysis, uncertainty about method of analysis of results)
1 (55) [60]	Patient perception of improvement	Topical tetracycline versus placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
What are the effects of oral treatments in people with acne vulgaris?									
1 (56) [62]	Acne severity	Oral erythromycin versus oral doxycycline	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (300) [63] [64] [65]	Acne severity	Oral erythromycin versus oral tetracycline	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct comparison between groups in one RCT
1 (200) [64]	Patient perception of improvement	Oral erythromycin versus oral tetracycline	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (113) [67] [68]	Acne severity	Oral doxycycline versus placebo	4	–3	0	–2	0	Very low	Quality points deducted for sparse data, incomplete reporting of results, and poor follow-up. Directness points deducted for no direct comparison between groups in one RCT and for low dose of doxycycline used in treatment arm of another RCT
1 (51) [68]	Patient perception of improvement	Oral doxycycline versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for low dose of doxycycline used in treatment arm
1 (28) [69]	Acne severity	Oral doxycycline versus oral oxytetracycline	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
4 (1081) [75] [74]	Acne severity	Oral minocycline versus placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for no direct comparison between groups
1 (64) [76]	Acne severity	Oral minocycline versus oral doxycycline	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (64) [76]	Patient perception of improvement	Oral minocycline versus oral doxycycline	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
3 (less than 348) [77] [78] [79]	Acne severity	Oral minocycline versus oral lymecycline	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting
2 (278) [77] [78]	Patient perception of improvement	Oral minocycline versus oral lymecycline	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting
1 (261) [80]	Patient perception of improvement	Oral minocycline versus oral oxytetracycline	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about clinical relevance of results

Important outcomes	Acne severity, Patient perception of improvement, Psychological distress, Quality of life								
Studies (Participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
2 (144) [73] [81]	Acne severity	Oral minocycline versus oral tetracycline	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (144) [81] [73]	Patient perception of improvement	Oral minocycline versus oral tetracycline	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for assessing different outcomes
7 (less than 621) [26] [57] [59] [88] [58] [89] [23]	Acne severity	Oral tetracycline versus placebo	4	–2	0	–1	0	Very low	Quality points deducted for incomplete reporting of results and methodological weaknesses (no intention-to-treat analysis and blinding flaws). Directness point deducted for no direct comparison between groups
2 (less than 392) [26] [23]	Patient perception of improvement	Oral tetracycline versus placebo	4	0	0	–1	0	Moderate	Directness point deducted for uncertainty about definitions of assessments
1 (33) [90]	Acne severity	Oral isotretinoin versus placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (29) [91]	Acne severity	Oral isotretinoin versus oral tetracycline	4	–1	0	0	0	Moderate	Quality point deducted for sparse data

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.